Improving complex cardiac implantable electronic device therapy outcomes

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Improving complex cardiac implantable electronic device therapy outcomes

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Abstract of Thesis

Cardiac resynchronisation therapy (CRT) devices and implantable cardioverter defibrillators (ICDs) are frequently implanted in patients with heart failure and those at risk of ventricular arrhythmia (VA). Approximately 30-50% of patients undergoing CRT implantation fail to derive any improvement, depending on heart failure aetiology and the metric used to evaluate response. Furthermore, appropriate ICD therapy only occurs in one third of patients implanted with an ICD indicating better risk stratification of VA is needed. This thesis therefore aims to explore novel ways to improve complex cardiac implantable electronic device therapy outcomes.

Initially, this thesis explores the feasibility and potential benefit of using real-time cardiac CT image overlay guidance and multisite left ventricular (LV) pacing as two distinct approaches to improve CRT response rates through optimal LV lead delivery. Real-time CT image overlay appears safe and feasible with significant improvements in echocardiographic volumetric response outcomes at 6-months follow-up compared to baseline. However, whilst multisite LV pacing appears feasible and safe, no evidence was found to support its use in improving CRT response in patients with left bundle branch block and intermediate QRS prolongation of 120-150 ms.

Finally, this thesis investigates the role of scar heterogeneity, quantified by mean entropy using cardiac magnetic resonance texture analysis (CMR-TA), as a potential metric for ICD risk stratification. For the first time, mean entropy, calculated using CMR-TA, was identified as an independent predictor of appropriate ICD therapy in patients with mixed cardiomyopathy and ischaemic cardiomyopathy-only, suggesting a potential

role in predicting VAs and risk stratifying patients for ICD implantation. Furthermore, lower scar heterogeneity, quantified by mean entropy using cardiac MRI texture analysis, was found to be associated with successful ATP whereas higher scar heterogeneity was associated with more aggressive VAs unresponsive to ATP requiring shock therapy.

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Declaration

I confirm the work within this thesis is my own and I have appropriately acknowledged the work of others.

Dr Justin S Gould

Acknowledgments

During this PhD, I have had the privilege of working with many talented individuals across a wide range of disciplines.

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Thesis outline

This thesis aims to explore novel strategies to improve complex cardiac implantable electronic device therapy outcomes.

Chapter 1 provides an introduction into the burden, aetiology and pathophysiology of heart failure. The use of cardiac resynchronisation therapy and ways to improve response rates are explored with a focus on image guidance and multisite left ventricular pacing. A detailed review on the evidence of chronic right ventricular pacing in patients with heart failure is included. In addition, Chapter 1 discusses the use of ICDs in the heart failure population and the importance of ICD risk stratification.

Chapter 2 explores the feasibility and potential benefit of using real-time cardiac CT image-overlay guidance to improve CRT response rates through targeting late mechanical activation for optimal LV lead delivery.

Chapter 3 assesses the feasibility and outcomes of multisite left ventricular pacing in patients with LBBB and an intermediate QRS duration of 120-150ms as a way to improve CRT response rates.

Chapter 4 evaluates the benefit of quantifying scar heterogeneity, using cardiac MRI texture analysis (mean entropy), as a potential metric to predict appropriate ICD therapy and explore its potential role in ICD risk stratification.

Chapter 5 builds upon the work in the previous chapter and examines mean entropy, calculated using cardiac MRI texture analysis, as a potential metric to predict ATP failure and explore its potential role in patient selection for ICD implantation.

Chapter 6 is a synthesis and summary of the findings from the preceding chapters. Final conclusions are made including a summary of the new knowledge acquired and recommendations for future directions.

Abbreviations

NYHA – New York Heart Association
MLWHFQ - Minnesota Living with Heart Failure Questionnaire
HFpEF – Heart failure with preserved ejection fraction
HFmrEF – Heart failure with mid-range ejection fraction
HFrEF – Heart failure with reduced ejection fraction
UK – United Kingdom
NHS – National Health Service
LV – left ventricular/left ventricle
ACEI – angiotensin converting enzyme inhibitor
CRT – cardiac resynchronisation therapy
ICD – implantable cardioverter-defibrillator
LBBB – left bundle branch block
RV – right ventricular/right ventricle
CIED – cardiac implantable electronic device
AV - atrioventricular
LVSD – left ventricular systolic dysfunction
HF – heart failure
LVEF – left ventricular ejection fraction
TTE – transthoracic echocardiogram
RVA – right ventricular apex
RVHS – right ventricular high septum
HBP – His bundle pacing
AF – atrial fibrillation
PPM – permanent pacemaker
SND – sinus node disease
LVESV – left ventricular end-systolic volume
LVEDD – left ventricular end-diastolic diameter
CRT-P – cardiac resynchronisation therapy pacemaker
CRT-D – cardiac resynchronisation therapy defibrillator
2D – two-dimensional
ESC – European Society of Cardiology
SHR – sub-hazard ratio
6MWT – six-minute walk test
MACE – major adverse cardiovascular event
ECG - electrocardiogram
CT – computed tomography
TriV – triventricular pacing
BiV – biventricular pacing
UT – Utah
NY – New York
CABG – coronary artery bypass graft
mL – millilitre
m – metre
pg – picogram
SR – sinus rhythm
ICM – ischaemic cardiomyopathy
MRI – magnetic resonance imaging
CA – California
USA – United States of America
WiSE - Wireless Stimulation Endocardially
CMR – cardiac magnetic resonance
LGE – late gadolinium enhancement
SSFP – steady state free precision
LMA – late mechanical activaton
VA – ventricular arrhythmia
VT – ventricular tachycardia
CMR-TA – cardiac magnetic resonance texture analysis
ATP – anti-tachycardia pacing
AHR – acute haemodynamic response
LVEDV – left ventricular end-diastolic volume
CTA – computed tomography angiogram
HU – Hounsfield units
DICOM - Digital Imaging and communications in medicine
AHA – American Heart Association
3D – three-dimensional
RAO – right anterior oblique
PA – posterior-anterior
LAO – left anterior oblique
CS – coronary sinus
NT-pro BNP – N-terminal pro-B type natriuretic peptide
SD – standard deviation
ARB – angiotensin receptor blocker
DLP – dose length product
LAD – left anterior descending (artery)
RA – right atrial/right atrium
DAP – dose area product
IQR – interquartile range
ESV – end-systolic volume
EDV – end-diastolic volume
SPECT – single photon emission computed tomography
MPI – myocardial perfusion imaging
ECGI – electrocardiogram imaging
NICM – non-ischaemic cardiomyopathy
FWHM – full-width half-maximum
SSF – spatial scale filter
VF – ventricular fibrillation
ROC – receive operator curve
CAD – coronary artery disease
SCD – sudden cardiac death
DCM – dilated cardiomyopathy
EP – electrophysiology
YIA – young investigator award

Chapter 1: Background and literature review

1.1 Heart failure

1.1.1 The prevalence of heart failure

Heart failure is frequently the final common pathway of many cardiovascular disorders[1,2] which accounts for a significantly large global burden of morbidity and mortality. Despite advances in our understanding and treatment of heart failure, it remains the commonest cause of death in the developed world and increasingly in the developing world. Heart failure is an overarching term used to define the syndrome that results from cardiac pump failure and the inability to effectively deliver oxygenated blood to organs and tissues, resulting in a series of physiological responses.[3–6] Patients frequently experience deteriorating breathlessness, exercise capacity and peripheral oedema with heart failure progression resulting in a significant deterioration in quality of life, although symptoms can sometimes be temporarily improved with heart failure treatment.[3] The New York Heart Association (NYHA) Functional Classification helps with staging of heart failure symptom severity and limitations for patients and are graded from Class I (mild) to IV (severe).[7] The Minnesota living with heart failure questionnaire (MLWHFQ) score further attempts to quantify the impact of heart failure on patient's activities of daily living.[8–10]

More recently, heart failure has been re-defined into three categories; heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) as shown in Table 1-1. This thesis will focus on HFrEF.

Table 1-1: Definitions of heart failure by left ventricular ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Reproduced with permission from Ponikowski et al 2016[11]

The most common causes of reduced cardiac function are hypertension, ischaemic heart diseases, valvular heart disease and non-ischaemic cardiomyopathies which may be inherited or acquired. Table 1-2 summarises the aetiologies of heart failure.

Heart failure prognosis is generally very poor with approximately 40% of patients dying within 12 months of being diagnosed, and it remains significantly worse compared to that of some malignancies.[12] Furthermore, only a third of patients with heart failure remain alive after heart failure diagnosis.[12]

Heart failure continues to pose a significant universal health problem with an estimated 26 million people affected by the condition.[13] In the United Kingdom (UK), the prevalence of heart failure is estimated to be up to 920,000 with approximately 200,000 new cases diagnosed each year.[14] Heart failure accounts for around 2% of the total National Health Service (NHS) budget in the UK and is expected to rise with an increasingly older population.[15] Even though survival from acute myocardial infarction has considerably reduced due to thrombolysis and primary percutaneous coronary intervention,[1617,18] a significant number of such patients still develop heart failure in their later years. Moreover, an increasing number of patients are being diagnosed with

chemo-induced cardiomyopathy due to certain cardiotoxic chemotherapy treatments with a corresponding reduction in cancer mortality rates.[19]

Table 1-2: The causes of heart failure

DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-Inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases.
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.
ABNORMAL LOADING CONDITIONS		
Hypertension		
Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
	Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
	Endomyocardial	HES, EMF, endocardial fibroelastosis.
High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
Volume overload		Renal failure, iatrogenic fluid overload.
ARRHYTHMIAS		
Tachyarrhythmias		Atrial, ventricular arrhythmias.
Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hypereosinophilic syndrome; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; LV = left ventricular.

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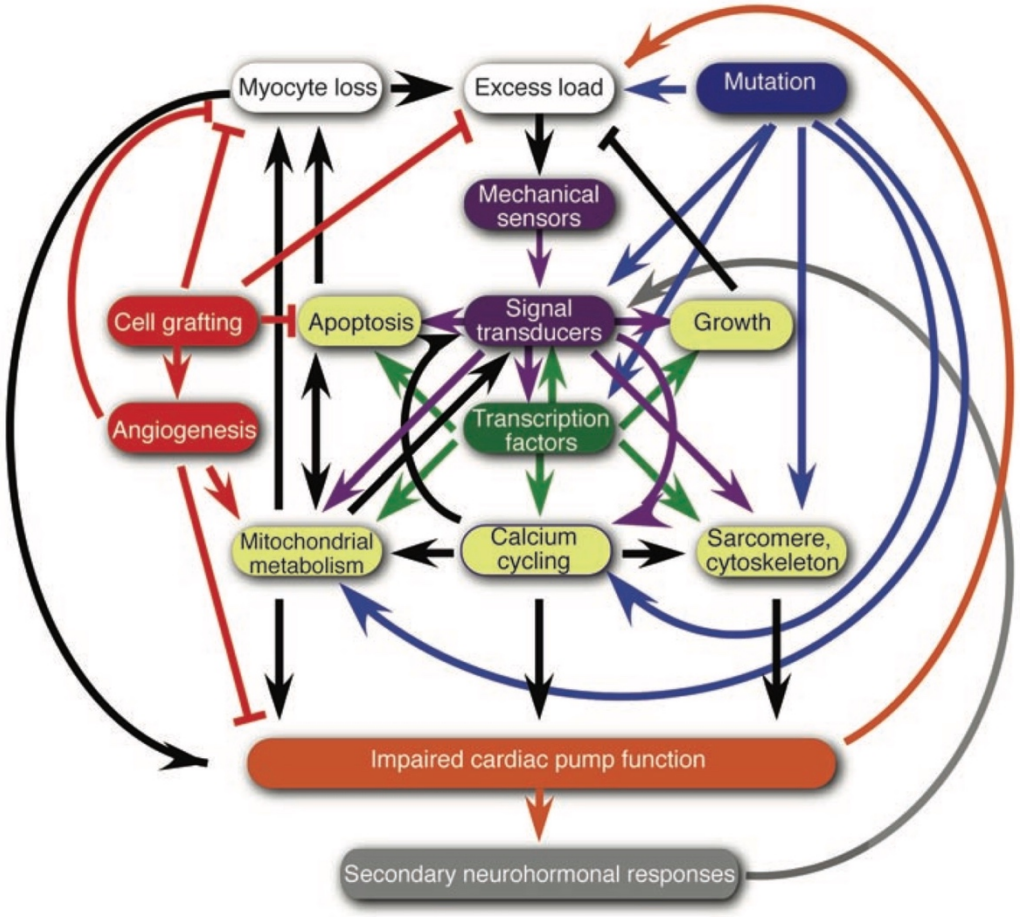
1.1.2 The pathophysiology of heart failure

The clinical manifestations of heart failure are caused by a cascade of biochemical, structural and haemodynamic changes that result in increased wall stress and ventricular remodelling initiating hypertrophy and dilatation of the left ventricle.[1,4,5,20] As a result, the failing LV is unable to meet metabolic demands and atrioventricular dyssynchrony results in a broadened QRS, frequently left bundle branch block and functional mitral regurgitation.[4,5,20]

These mechanisms lead to impairment of LV filling and/or contractility with subsequent activation of neurohormonal pathways, frequently resulting in the clinical manifestations of the heart failure syndrome.[21] Interestingly, the clinical syndrome of heart failure may occur rapidly after acute myocyte injury or develop over weeks, months or even years or in some circumstances not at all. Figure 1-1 demonstrates the complex interplay of biological mechanisms in heart failure.



Reproduced with permission from Benjamin and Schneider 2005[21]

Figure 1-1: A partial wiring diagram of biological circuits for heart failure.

'Impaired pump function after myocyte death from myocardial infarction or abnormal loading conditions such as found in hypertension (white) activate a biomechanical stress-dependent signalling cascade (purple). The responsible targets of altered signal transduction cascades in heart failure include transcription factors, coactivators, and corepressors for cardiac gene expression (green) as well as the effector mechanisms like calcium cycling, metabolism, growth, and apoptosis (yellow) that culminate in ventricular dysfunction (orange) and secondary neurohormonal responses (grey) such as adrenergic drive and intramyocardial growth factors (not shown). Inherited mutations for cardiomyopathy (blue) affect proteins at many of these points and are thought to engage a similar cascade of events in order to elicit the full myopathic phenotype. Cell based therapies (red), although often envisioned working chiefly or wholly by replacing dead myocytes, probably improve ventricular performance through a combination of mechanisms, including angiogenesis, paracrine signals for myocyte protection and conceivably augmenting host self-repair.'[21]

Following myocyte injury, initial adaptation to maintain stroke volume occurs as described by the Frank-Starling law.[22,23] The response to a reduction in blood ejected from the left ventricle is two-fold: A rise in the LV end diastolic volume and pressure results in an increase in preload. This stimulates greater stretch of the myocytes resulting in an increased recoil force of contraction to restore the decrease in stroke volume. Neurohormonal responses gradually ensue to help maintain cardiac output by increasing the LV end diastolic pressure through sodium and water retention. To begin with, these mechanisms are protective but the continuous onslaught of raised filling pressures and chronic arterial wall constriction lead to ventricular remodelling and eventually LV pump failure.[24] When myocyte death occurs through either apoptosis or necrosis, an inflammatory soup, mediated by the release of cytokines leads to ventricular wall thinning and chamber dilation.[25,26] At a cellular level, activation of enzymes leads to destruction of the extracellular matrix which may condition the progression of the cardiac myopathy.[25,26] In addition, myocardial fibrosis occurs from proliferation of collagen synthesis.[25,26]

Continuous interplay and progression of the above pathological processes leads to the clinical manifestation of heart failure described above.

1.1.3 Pharmacotherapy options for heart failure with reduced ejection fraction

Treatment goals for patients with heart failure are primarily focussed on improving quality of life, functional capacity, clinical status, preventing hospital admissions and reducing mortality.[11]

A treatment workflow for treating heart failure with reduced ejection fraction is shown in Figure 1-2.

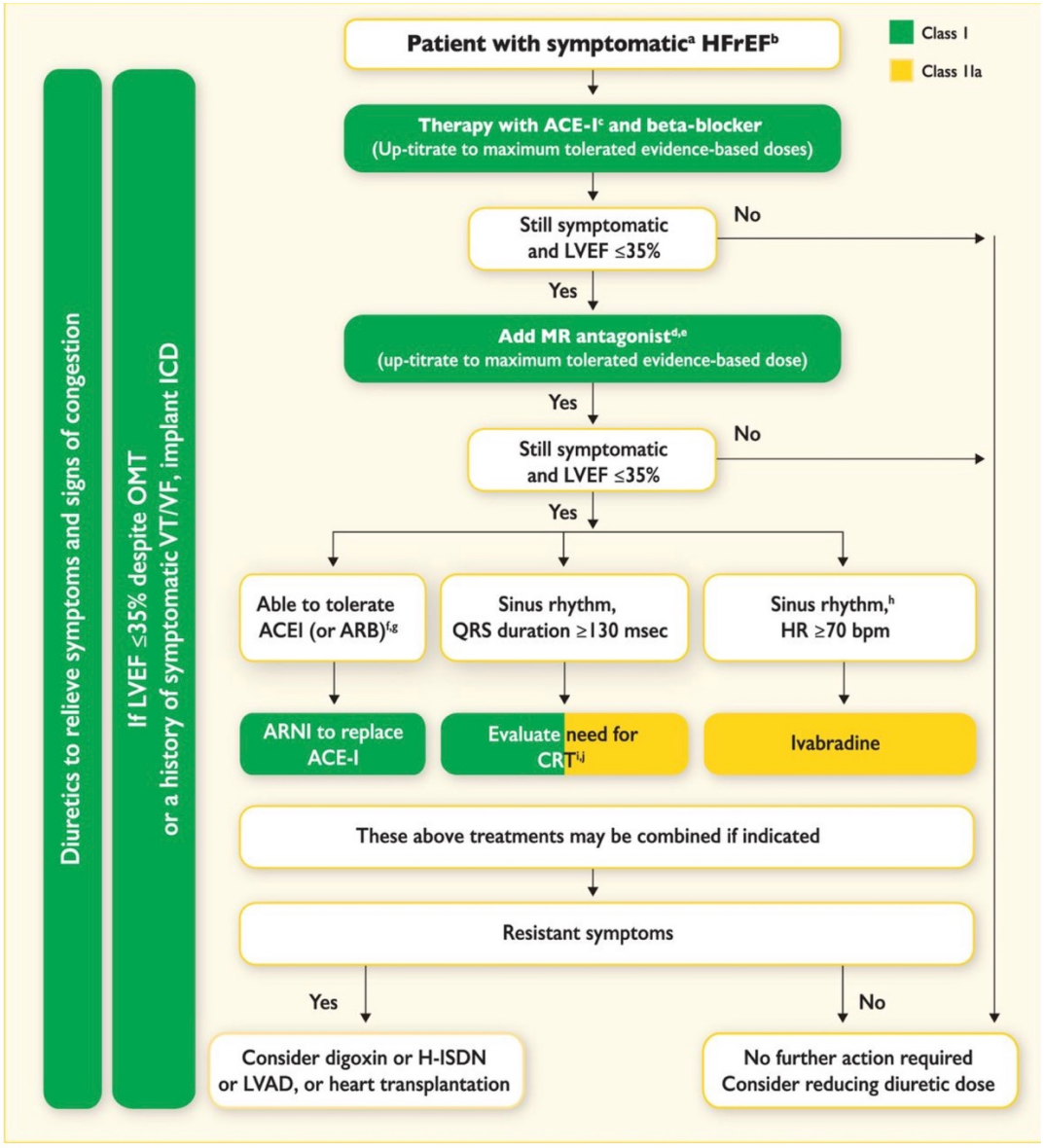


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Figure 1-2: Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction.

'Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronisation therapy;

HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. Symptomatic = NYHA Class II-IV. HFrEF = LVEF <40%. If ACE inhibitor not tolerated/contra-indicated, use ARB. If MR antagonist not tolerated/contra-indicated, use ARB. With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/ml or NTproBNP > 500 pg/ml in men and 750 pg/ml in women). With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). In doses equivalent to enalapril 10 mg b.i.d. With a hospital admission for HF within the previous year. CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm). CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in atrial fibrillation provided a strategy to ensure bi-ventricular capture in place (individualized decision). For further details, see Sections 7 and 8 and corresponding web pages.'[11]

Neuro-hormonal antagonists improve survival in patients with heart failure with reduced ejection fraction and are recommended for all patients with the condition unless intolerant or contraindicated. These included angiotensin converting enzyme inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs) and beta-blockers.

More recently, the PARADIGM-HF trial demonstrated that the combination of an angiotensin receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril) is superior to an ACEI (enalapril) in reducing the risk of mortality and heart failure hospitalisation.[11,27] Sacubitril/valsartan is currently recommended to replace ACEIs in mobile patients with heart failure with reduced ejection fraction who remain symptomatic despite optimal pharmacotherapy and who match the PARADIGM-HF trial criteria.[11,27] Angiotensin receptor blockers (ARBs) have in the past been reserved for

patients who are intolerant to an ACEI but they have not been consistently proven to reduce mortality in patients with heart failure with reduced ejection fraction.[11] Ivabradine reduces the raised heart rates seen in patients with heart failure and has also been shown to improve outcomes.[11] Diuretic medications are used in patients with symptoms and/or signs of congestion and in conjunction with the above medications that have been shown to improve prognosis.[11]

In addition to optimal pharmacotherapy, cardiac implantable electronic devices (CIEDs) for certain patient groups have shown an incremental mortality reduction at two years follow-up.[28]

1.1.4 Cardiac resynchronisation therapy for heart failure

In 1995, Cazeau et al. described the first use of biventricular (BiV) pacing for a patient with heart failure.[29] This rapidly evolved into CRT as a treatment for selected patients with heart failure. Delivering continuous electrical impulses to both ventricles has been shown to restore electromechanical dyssynchrony and improve cardiac output. In certain groups of patients with heart failure (Table 1-3), CRT has been shown to improve both symptoms and quality of life,[11,30] as well as reduce morbidity and mortality.[4,31–33] It remains unclear whether CRT reduces the arrhythmia burden in heart failure patients, thereby reducing the need for an ICD.[11] Similarly, it is currently uncertain if CRT offers incremental benefit to an ICD by reducing mortality rates from deteriorating heart failure, leading to longer exposure to the risk of arrhythmia.[11]

Table 1-3: Indications for CRT

Recommendations	Class [a]	Level [b]	Ref [c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

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'SR: sinus rhythm, AF: atrial fibrillation, Sx: symptoms, OMT: optimal medication therapy, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association grade of symptoms, BVp: biventricular pacing, LBBB: left bundle branch block, IVamb: NYHA class IV ambulatory, RVp: right ventricular pacing, PPM: permanent pacemaker, ICD: internal cardiac defibrillator, HF: heart failure. *recent change to European heart failure guidelines in August 2016.[11]

The COMPANION[32] and CARE-HF trials[4,34] demonstrated the advantages of CRT compared to optimised medical therapy alone. However, not all patients respond to CRT as well as others.[11,30] One of the most important mechanisms of action of CRT is reverse remodelling which is likely to underpin the improvements in morbidity and mortality.[11] Ischaemic cardiomyopathy (ICM) is frequently associated with LV scar (myocardial fibrosis) which may be subendocardial or transmural and less likely to undergo significant reverse remodelling.[11,35]

Patients with true left bundle branch block (LBBB) morphology are more likely to respond favourably to CRT, compared to non-LBBB morphology.[11] However, this may reflect the fact that patients with LBBB morphology typically have longer QRS durations and whether this or QRS morphology is the main driver of a favourable response to CRT remains to be decided.[11]

Chronic right ventricular (RV) pacing in the setting of impaired LV systolic function may worsen cardiac dyssynchrony and is an important consideration for all patients receiving a CIED as well those with pre-existing devices. This may be prevented by CRT and lead to improved patient outcomes.[36–39] However the evidence remains uncertain and given this is an increasingly common conundrum when treating patients with heart failure, this will be covered in depth in the next section.

This section has been adapted from *Chronic Right Ventricular Pacing in the Heart Failure Population.*[40]

1.2 Improving the outcomes of chronic right ventricular pacing in the heart failure population

1.2.1 Introduction

Right ventricular (RV) pacing is an important and effective treatment in patients with atrioventricular (AV) block. RV pacing restores the heart rate to a pre-determined rate however, a high RV apical pacing percentage/burden may promote left ventricular systolic dysfunction (LVSD).[41–49] Alternative RV pacing sites have been explored to combat this problem as well as investigating CRT in patients with AV block with mild to severe heart failure. CRT is an effective therapy to improve symptoms and reduce mortality in patients with dyssynchronous heart failure.[50] CRT has consistently demonstrated benefit in treating patients with systolic heart failure and interventricular conduction delay, typically with LBBB.[4,32,51] However, numerous trials have used moderate and high degree AV block in their exclusion criteria to independently evaluate the effects of CRT without the potential cofounding detrimental effects of RV pacing.[37] Notwithstanding, several studies have demonstrated the deleterious effects of RV apical pacing and therefore alternative RV pacing sites have been explored as well as using CRT for patients with narrow QRS and/or mild to moderate heart failure in patients who are predicted to require a significant amount of RV pacing.[52] In the present review, we

review the trials that have demonstrated potentially harmful effects from RV apical pacing as well as reviewing the evidence of alternative RV pacing sites and CRT for patients who have heart failure and AV bock (Block HF and BioPace trials).

1.2.2 Chronic Right Ventricular Pacing and its Deleterious Effects

Single or dual chamber RV pacing is the mainstay of treatment for symptomatic AV block. However, there is increasing evidence of potential adverse effects with chronic RV apical pacing secondary to mechanical and electrical dyssynchrony.[53,54] The detrimental effects from chronic RV pacing including the manifestation of heart failure, adverse LV remodelling and LVSD have repeatedly been reported.[41–49] These include a wide array of structural changes incorporating left atrial and LV remodelling, LV wall thickness and functional mitral regurgitation.[55–58] In patients with complete AV block, both cellular and intracellular changes have been described including degenerative fibrosis.[59] The Dual Chamber and Implantable Defibrillator (DAVID) Trial enrolled patients undergoing ICD implantation without bradycardia or AV block and randomized them to either DDD pacing at 70 beats/min or VVI backup pacing at 40 beats/min. The DAVID trial identified significantly more heart failure and cardiovascular events in the DDD group with a higher percentage of RV apical pacing.[45] Similarly, the Mode Selection Trial (MOST) demonstrated that RV apical pacing may lead to heart failure, however, the loss of AV synchrony itself was shown to probably be less important. The MOST investigators found a significantly increased risk of heart failure events in both single and dual chamber pacing modes, with a threshold for adverse outcomes with an RV pacing percentage greater than 40%.[52,60] The Multicenter Automated Defibrillator Implantation Trial (MADIT II) randomized patients with ischemic cardiomyopathy and

LVEF ≤30 % to ICD therapy versus (vs.) conventional medical therapy. MADIT II showed that ICD therapy reduced total mortality.[61] A subsequent subanalysis showed that patients with a high RV pacing percentage had a significantly increased risk of new or worsening heart failure.[61,62] The potentially harmful effects of long-term RV pacing may occur in patients with both preserved and reduced LV systolic function, however, they are more prominent in patients with a reduced LVEF at baseline. The true incidence of LV remodelling secondary to RV apical pacing is not known, however, it is widely recognized to occur where RV pacing is >40 % of the time.[60] However, there are some pacing dependent patients who have 100% RV pacing who do not develop LV dysfunction for reasons that are unknown.[63]

1.2.3 Pathophysiology of the Detrimental Effects of Right Ventricular Pacing

Several clinical studies have established the potential adverse effects of chronic RV pacing on LV function. The exact pathophysiological process underpinning the deleterious effects from chronic RV pacing is not clear. RV apical pacing may have adverse effects on haemodynamics, remodelling, mechanical function, myocardial metabolism and perfusion due to mechanical and electrical dyssynchrony.[52,64,65] An LBBB-type pattern is widely recognised to develop immediately following RV apical pacing. Early activation of the RV apex subsequently causes mechanical dyssynchrony as well as increasing early systolic shortening which results in pre-stretch of the late-activated regions and subsequent premature relaxation.[52,66,67] As a result, changes in LV mechanical and electrical activation due to RV apical pacing may lead to a decrease in cardiac output as well as intraventricular and interventricular dyssynchrony resulting in

LVSD. This has been demonstrated in a number of studies using doppler and strain analysis on two-dimensional (2D) and three-dimensional (3D) transthoracic echocardiogram (TTE).[48,52,64,65,67–71] In addition, reduced ventricular diastole and increased ventricular systole may lead to reduced coronary perfusion.[52] Interestingly, with chronic RV apical pacing, up to 65% of patients have been found to have myocardial perfusion defects in the pacing region in the absence of flow-limiting coronary artery disease.[72–74]

1.2.4 Alternate Right Ventricular Pacing Sites

The advent and safety of active fixation leads has facilitated the exploration of alternatives to the traditional apical RV pacing site. However, using other RV pacing sites such as RV outflow tract and septal pacing on their own, may not be sufficient to circumvent the detrimental effects of chronic RV pacing. This might be explained by technical difficulties with lead placement as well as no clear evidence of superiority of RV high septal pacing, not to mention evidence of worsening LVEF with any RV pacing site.[52] The PROTECT-PACE study randomized 240 patients with high-grade AV block requiring >90% ventricular pacing and preserved baseline LVEF >50%, to receive pacing at the right ventricular apex (RVA) (n = 120) or right ventricular high septum (RVHS) (n = 120). At 2 years, LVEF decreased in both the RVA (57 ± 9 to 55 ± 9%, P = 0.047) and the RVHS groups (56 ± 10 to 54 ± 10%, P = 0.0003).[75] However, there was no significant difference in intra-patient change in LVEF between confirmed RVA and RVHS lead position (P = 0.43).[75] Similarly, there were no significant differences in heart failure hospitalization, mortality, burden of atrial fibrillation, or plasma brain natriuretic peptide levels between the two groups.[75] A significantly greater time was required to

place the lead in the RVHS position (70 ± 25 vs. 56 ± 24 min, P < 0.0001) with longer fluoroscopy times (11 ± 7 vs. 5 ± 4 min, P < 0.0001). The authors concluded that in patients with high-grade AV block and preserved LV function requiring a high percentage of ventricular pacing, RVHS pacing does not provide a protective effect on LV function over RVA pacing in the first 2 years.[75]

His bundle pacing (HBP) is an alternative way to perform bradycardia pacing. The His-Purkinje conduction system allows the impulse generated by the sinoatrial node to rapidly propagate into both right and left ventricles which facilitates synchronized ventricular contraction. Early studies demonstrated distal HBP was able to normalize bundle branch block and QRS morphology.[76] The first successful series of permanent direct HBP was performed in 18 patients with atrial fibrillation (AF) and dilated cardiomyopathy in 2000 where the investigators found improvements in LV dimensions and cardiac function.[77] HBP may provide physiological activation thereby avoiding ventricular dyssynchrony and preserving LV systolic function in patients with a narrow QRS duration and several studies have suggested a potential beneficial effect over RV pacing.[78–82] HBP may therefore be a way to avoid the potential deleterious effects of RV pacing, however, further randomized studies including The His Optimised Pacing Evaluated for Heart Failure (HOPE-HF) trial will be important in determining this.

Table 1-4: CRT versus right ventricular pacing trials in patients requiring bradycardia pacing

Study	*n*	Inclusion Criteria	Treatment	Follow-up	End Point	Results
PAVE [36]	184	Persistent AF and AV node ablation	CRT group (n=81) RV group (n=81)	6 mths	LVEF 6MWT distance	RV group reduction 6MWT distance (p=0.04) & LVEF (*p*=0.03) vs CRT.
Ablate and Pace in AF [38]	186	Persistent/permanent AF	CRT (n=97) RV (n=89)	Median 20 mths	Composite primary end point: Death from HF, hospitalization for HF or worsening HF	Composite Primary end point CRT 11% vs. RV Group 26% (*p* = 0.005). CRT group less worsening HF (*p* = 0.0001) & less HF hospitalizations.
DAVID [45]	506	Dual chamber ICD indication	ICD VVI 40 bpm (back up pacing) (n=256) ICD DDDR 70 bpm (n=250)	Median 8.4 mths	Composite primary end point: Death from HF or first hospitalization for HF.	One-year survival free of composite end point 83.9% patients with VVI-40 vs 73.3% for DDDR-70 (relative hazard, 1.61; CI 95%, 1.06-2.44).
MOST [60]	2010	PPM for Sinus node dysfunction	Single chamber VVIR pacing (n=632) vs DDDR pacing (707) for SND	Median 33.1 mths	HF hospitalization & AF	RV pacing DDDR mode >40% time led to 2.6-fold increased risk HF hospitalization vs. lower % pacing (normal baseline QRS duration, despite preservation of AV synchrony, in SND patients).
PREVENT HF [83]	108	Indication for pacing with LVEF >50% & expected RV pacing of ≥80%	CRT (*n*=50) RV apical (*n*=58)	12 mths	LVEDV	No significant difference between CRT & RV pacing in LVEDV. No change in LVEF, LVESV or HF events.
PACE [84]	177	LVEF ≥ 45% Standard bradycardia indications for pacing	CRT (*n*=89) RV apical (*n*=88)	Up to 2 years	LVESV LVEF	LVESV & LVEF deteriorated in RV apical group vs no change CRT group, significant difference of 9.9 % points between groups at 2-year follow-up (*p*< 0.001).
HOBIPACE [85]	30	Permanent RV pacing indication LVEDD ≥60 mm LVEF ≤ 40%	Run-in phase then randomised to 3 mths RV pacing then 3 mths CRT or vice-versa.	3 mths with crossover to complimentary pacing mode	LVESV LVEF Peak oxygen consumption	Greater improvement in QoL, LVEF, maximal & submaximal exercise capacity CRT group vs RV pacing group.
COMBAT [86]	60	Standard RV pacing indication for AV block LVEF ≤ 40%, NYHA II-IV	Group A: RV pacing, then CRT, then RV pacing. Group B: CRT, then RV pacing, then CRT.	Minimum 3 mths each mode	NYHA class & QoL score	In patients with systolic HF & AV block requiring permanent ventricular pacing, CRT was superior to RV pacing.

Study	*n*	Inclusion Criteria	Treatment	Follow-up	End Point	Results
BLOCK HF [37]	691	AV block 1st -3rd HF NYHA I-III LVEF ≤50%	CRT (n=349,) RV pacing (n=342).	Mean 37 mths	Composite primary end point: time to death any cause, urgent care visit for HF requiring IV Rx, or ≥15% increase LVESV index.	Primary outcome 190/342 pts (55.6%) RV pacing group, vs 160/349 pts (45.8%) in CRT group. CRT group significantly lower incidence primary outcome vs RV pacing group (HR, 0.74; 95% credible interval, 0.60-0.90).
BioPace Preliminary Results [87]	1810	Indication for ventricular PPM according to guidelines or anticipated high frequency of V pacing	CRT (n=902) RV pacing (n=908)	Mean 5.6 years	Composite primary end point: First hospitalization due to heart failure or time to death	No statistically significant difference between CRT and RV pacing for composite primary end point (preliminary results).
Protect PACE [75]	240	High-grade AV block requiring >90% RV pacing with preserved LVEF >50%	RV apical pacing (n=120) RVHS pacing (n=120)	2 years	Intra-patient change in LVEF	At 2 years, LVEF decreased in both RV apical (57 ± 9 to 55 ± 9%, P = 0.047) & septal groups (56 ± 10 to 54 ± 10%, P = 0.0003). No significant difference in intra-patient change LVEF between confirmed apical & septal lead position (P = 0.43).

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Abbreviations

HF = heart failure, LVEDV = left ventricular end-diastolic volume, CRT = cardiac resynchronisation therapy, RV = right ventricular, AF = atrial fibrillation, CI = confidence interval, SND = sinus node dysfunction, QoL = quality of life, AV = atrioventricular, LVESV = left ventricular end-systolic volume, HR = hazard ratio.

There have been several studies examining CRT-based approaches to avoid the detrimental effects of apical RV pacing in patients with AV block and normal, mild or moderate LVEF. PACE, PREVENT HF and BLOCK HF have all directly compared CRT with RV pacing in patients with an indication for bradycardia pacing who were likely to require a high percentage of RV pacing (Table 1-4). These studies recruited patients in both sinus rhythm and AF. CRT has been shown to have advantages over RV pacing in four randomised clinical trials.[36–38,89,90] There have also been smaller trials that have

demonstrated an advantage of CRT pacing over RV pacing.[70,85,86] However, both BioPace and PREVENT HF have not been able to demonstrate a statistically significant benefit of CRT pacing over RV pacing in similar cohorts.[83,87,91] All other trials included in Table 1-4 have shown CRT pacing to favour over RV pacing, irrespective of NYHA class, baseline LV systolic function, degree of reverse remodelling or QRS duration.[63]

The Pacing to Avoid Cardiac Enlargement (PACE) trial was a prospective, double-blinded, randomized, multicentre study where patients with bradycardia and preserved LVEF were randomized to receive CRT ($n = 89$) or RV apical pacing ($n = 88$).[84] Co-primary endpoints were LVEF and left ventricular end-systolic volume (LVESV) measured by 2D TTE. Patients were followed-up with a mean duration of 4.8 ± 1.5 years (2.5 – 7.8 years) and analyses of the primary endpoint were performed in 146 patients (CRT group n = 72, RV apical pacing group n = 74). The LVESV and LVEF remained unchanged in the CRT group whereas in the RV apical pacing group, not only did the LVEF decrease, the LVESV also increased progressively at follow-up.[84] The differences in LVEF between the RV apical pacing and CRT pacing groups were –6.3% at 1 year, –9.2% at 2 years and –10.7% at long-term follow-up (all $P < 0.001$). The corresponding differences in LVESV were +7.4 millilitres (mL) at 1 year, +9.9mL at 2 years and +13.1 mL at long-term follow-up (all $P < 0.001$).[84] In addition, the detrimental effects of RV apical pacing consistently occurred in all pre-defined subgroups (age groups, gender, QRS duration, pre-existing LV diastolic dysfunction, as well as pre-existing diabetes, hypertension and coronary artery disease). Patients in the PACE trial with RV apical pacing had a significantly higher prevalence of heart failure hospitalization than the CRT group (23.9% vs. 14.6%, log-rank $\chi^2 = 7.55$, $P = 0.006$).[84] The authors concluded that CRT was superior to RV apical pacing in the prevention of LV adverse remodelling and reduction of LVEF at 1 and 2 years

follow-up. The Homburg Biventricular Pacing Evaluation (HOBIPACE) and the Conventional Versus CRT Pacing in Heart Failure and Bradyarrhythmia Therapy (COMBAT) studies were both small randomized studies that found CRT pacing superior to conventional RV apical pacing in terms of improvement in quality of life, exercise capacity and LVEF as well as reduction in LV volumes.[49,85,86] HOBIPACE was a prospective, randomized crossover study where 30 patients, who had AV block, LVSD defined by an left ventricular end-diastolic diameter (LVEDD) ≥60 mm and an LVEF ≤40% with NYHA II-IV, were randomized to three months of RV pacing then three months of CRT pacing or vice-versa.

The COMBAT trial was a prospective, multicentre, randomized, double blind crossover study that enrolled 60 patients with pacing indications for AV block with an LVEF <40% and NYHA class II-IV for a mean follow-up period of 17.5 ± 10.7 months. All patients underwent CRT device implantation and were randomized to two groups and received the following for 3 months: Group A received RV pacing-CRT pacing-RV pacing and group B received CRT pacing-RV pacing-CRT pacing. There were significant improvements in LVEF, LVESV, NYHA class and quality of life questionnaire scores in the CRT group compared to the RV pacing group. Death was more frequent with RV pacing, however, six-minute walk test (6MWT) distance and VO_{2max} were not significantly different between the two groups.[86]

1.2.5 BLOCK-HF and BioPace Studies

To date the most significant study to assess the benefits of CRT over RV pacing is the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial. This was a large, multicentre, double-blind randomized study that assessed whether CRT reduced adverse LV remodelling, morbidity and mortality in patients with AV block with a standard class I or IIa indication for ventricular pacing, NYHA I-III class heart failure and LVEF ≤50%.[37] Patients received a cardiac resynchronisation therapy pacemaker (CRT-P) unless they had an indication for defibrillation therapy in which case they received a CRT implantable cardioverter-defibrillator (CRT-D) and were randomized to receive either CRT pacing or standard RV pacing. Patients with standard indications for CRT, based on the guidelines during the recruitment phase, were excluded from recruitment as were patients with recent or acute myocardial infarction, unstable angina, percutaneous or surgical coronary revascularization within 30 days or severe valvular heart disease with an indication for repair or replacement.[37,52] The primary outcome was time to death from any cause, ≥15% increase in LVESV index or an urgent care visit for heart failure that required intravenous therapy. 918 patients were enrolled, but only 691 patients underwent randomization in a 1:1 ratio. Patients were followed-up every 3 months with a mean follow-up duration of 37 months. The primary outcome occurred in 190 of 342 patients (55.6 %) in the RV pacing group and 160 of 349 (45.8 %) in the CRT group (hazard ratio, 0.74; 95% credible interval, 0.60 to 0.90). with a posterior probability of a hazard ratio <1 was 0.9978, exceeding the threshold of 0.9775 for a significant different between the two groups Figure 1-3.[37] Similar findings were noted in patients receiving a CRT-P or CRT-D. Removing the echocardiographic volumetric indices from the analysis, death from

any cause or an urgent care visit for heart failure still showed a significant difference in favour of CRT pacing compared to RV pacing with a hazard ratio of 0.73 (95 % credible interval, 0.57 to 0.92).[37,52] Of note, 6.4% of patients had a complication documented secondary to LV lead implantation. A subsequent sub-study of BLOCK HF demonstrated reverse remodelling within the CRT group using 2D TTE, where CRT pacing significantly reduced intraventricular mechanical delay and LV volume indices along with improvement in LVEF compared to RV pacing, all indicating LV revere remodelling. The risk of morbidity and mortality was estimated to increase by up to 1% for every 1mL/m^2 increase in LVESV index, suggesting LVESV index may be predictive of morbidity and mortality.[92] The main limitation of BLOCK HF was a high crossover rate from the RV pacing group to CRT group as well a reasonably large amount of missing 2D TTE data.

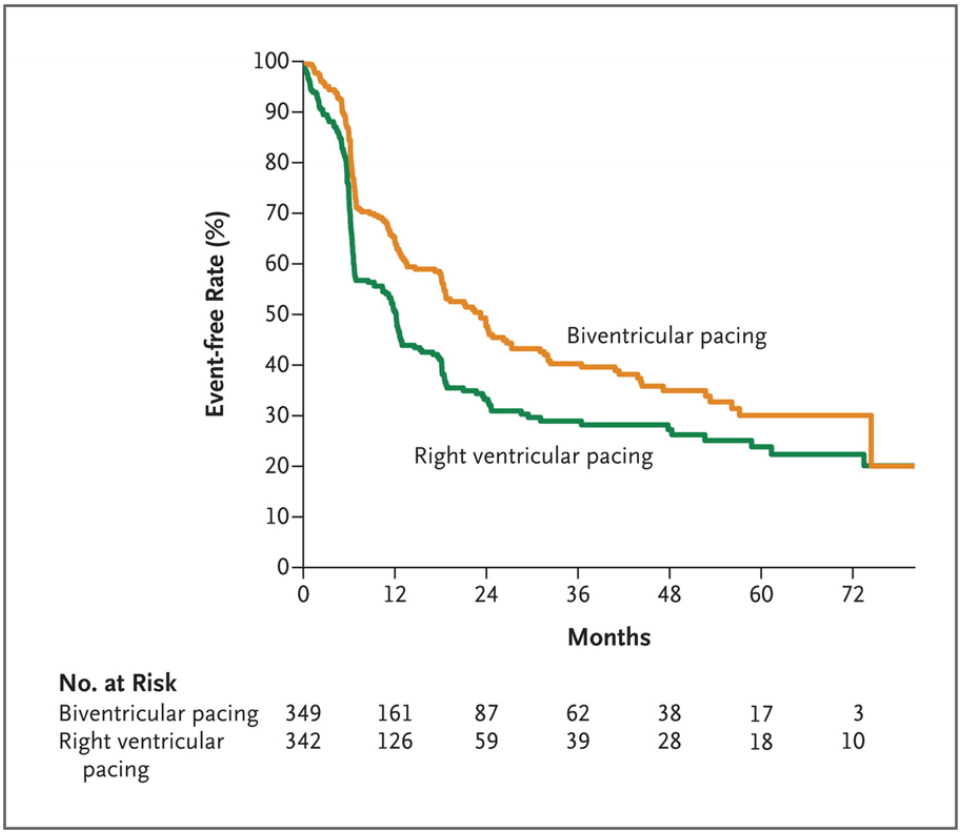

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Figure 1-3: Freedom from composite primary endpoint (time to death from any cause, ≥15% increase in LVESV index or an urgent care visit for heart failure that required intravenous therapy) in the BLOCK HF Trial.

The preliminary results of the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronisation (BioPace) trial were announced in 2014.[87,91] BioPace was a multicentre, randomized, single-blind study conducted in Europe and aimed to investigate the hypothesis that CRT pacing is superior to RV pacing in patients with AV block requiring permanent ventricular pacing. The combined primary end point was first hospitalization secondary to heart failure or time to death. Main inclusion criteria were patients with an indication for implantation of a ventricular pacemaker according to European Society of Cardiology (ESC) guidelines and an anticipated need for frequent ventricular pacing with any LVEF as measured by TTE. Patients with first, second and third AV block were enrolled. For first degree AV block, the defining PR interval was ≥220 milliseconds (ms) with an indication for pacing. Patients with permanent AF were also included providing their spontaneous ventricular rate was ≤60 beats per min at rest. 1810 patients were recruited and 902 patients were assigned to the CRT group and 908 to the RV pacing group. The patient demographics were largely similar to BLOCK HF except the average LVEF in BioPace was 55% compared to approximately 40% in Block HF. The preliminary results from BioPace showed no statistically significant difference between CRT pacing and RV pacing for first hospitalization secondary to heart failure or time to death. However, there was a non-significant trend in favour of CRT pacing versus RV pacing. Additional analyses might identify subgroups of patients where CRT pacing shows a clear and statistically significant benefit. Interestingly, LVEF did not seem to

have any influence on the combined primary outcome as the results were similar for LVEF ≤50% versus >50%. It is not immediately obvious why the BioPace study results differed to BLOCK HF, however, different patient demographics are likely to have played a role. Furthermore, patients in the BLOCK HF trial had a greater number of patients with LBBB (total 32.6%, CRT pacing group 35.2%, RV pacing group 29.8%) compared to BioPace (total 17.2%, CRT group 16.6%, RV group 18.3%) and lower LVEF, possibly indicating a cohort with more severe heart failure. Furthermore, AF is a recognised marker for underlying morbidity and again more patients in the BLOCK HF trial had AF (total 52.8%, CRT group 51.6%, RV group 54.1%) versus BioPace (total 24.9%, CRT group 24.9%, RV group 24.8%) indicating the higher morbidity in the BLOCK HF cohort. The long-awaited final published results from the BioPace investigators may help to better understand the results and differences to the BLOCK HF trial.

1.2.6 The Role of CRT in Patients with Atrial Fibrillation Undergoing AV Node Ablation

There have been several studies that have demonstrated better outcomes with CRT followed by AV node ablation than RV pacing in patients with symptomatic AF with rapid ventricular response.[36,38,39,93,94] In 2012, a meta-analysis of the aforementioned studies as well as two other similar studies found CRT pacing was associated with a significant reduction in hospitalizations for heart failure (RR= 0.38, 95%CI = 0.17–0.85; P = 0.02). Moreover, they established a non-significant reduction in mortality compared to RV pacing (RR= 0.75, 95 % CI = 0.43–1.30; P = 0.30).[39] Conversely, there was no significant difference in MLWHFQ Score or 6MWT distance between CRT and RV pacing groups. In

2010, Orlov et al. randomized 153 patients in a single-blinded trial and revealed a significant increase improvement in LVEF in the CRT pacing group, however, in the RV pacing group there was a non-significant reduction in LVEF.[94] Similarly, Brignole et al. conducted a prospective, multicentre study (The Ablate and Pace in AF Trial) and randomized 186 patients who had undergone CRT device implantation and AV node ablation to receive either CRT (n=97) with V-V interval optimization or RV apical pacing. Baseline demographics were similar to the PAVE study and follow-up was a median of 20 months (interquartile range 11-24). The primary composite endpoint of death from heart failure, hospitalization due to heart failure, or worsening heart failure occurred in 11% patients in the CRT group and 26% patients in the RV group [CRT vs. RV group: sub-hazard ratio (SHR) 0.37 (95% CI 0.18-0.73), P = 0.005].[38] Fewer patients had worsening heart failure in the CRT group compared to the RV group [SHR 0.27 (95% CI 0.12-0.58), P = 0.001] and fewer hospitalizations for heart failure [SHR 0.20 (95% CI 0.06-0.72), P = 0.013].[38] There was, however, no significant difference in total mortality, although the authors concluded that CRT was superior to RV apical pacing in reducing the clinical manifestations of heart failure in patients requiring an AV node ablation for symptomatic AF.[38] The Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (The PAVE study) was a prospective randomized controlled study that compared CRT pacing with RV pacing in 184 patients with NYHA functional class I to III heart failure (baseline LVEF 45% ± 15% in the CRT group vs. 47% ± 16% in the RV group) undergoing an AV node ablation for AF refractory to pharmacotherapy.[36] Patients undergoing ICD implantation were excluded. The PAVE study showed that patients randomized to CRT (n=103) had significant improvements in LVEF and 6MWT but not in quality of life parameters compared to the RV paced group. At 6 months post ablation, patients treated with CRT had a significant degree of improvement in 6MWT,

31% above baseline (82.9 ± 94.7 m), compared to patients receiving RV pacing, 24% above baseline (61.2 ± 90.0 m) (P = 0.04).[36] At 6 months post ablation, the LVEF in the CRT group (46%±13%) was significantly greater in comparison to the RV pacing group (41% ± 13%, *p* = 0.03).[36] The LVEF remained stable for patients in the CRT group whereas in the RV pacing group, the LVEF deteriorated by 3.1% at 6 weeks (*p* = 0.04) and 3.7% at 6 months (*p* = 0.03).[36] He authors concluded that CRT provided a significant improvement in 6MWT distance and LVEF compared to RV pacing in patients undergoing AV node ablation for AF. Furthermore, patients with LV systolic impairment or symptomatic heart failure derived the greatest benefit from CRT pacing.[36]

BLOCK HF was a landmark United States-based trial that revealed encouraging evidence that improved outcomes may be achieved with CRT pacing compared to RV apical pacing in patients with LVSD and AV block when a high percentage of RV pacing is anticipated.[49,52] As a result, in 2014 the United States Food and Drug Administration approved the use of CRT in patients with AV block associated with a high percentage of ventricular pacing, mild to moderate heart failure and LVEF ≤50%.[95] In 2016, the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure were updated recommending CRT over RV pacing for patients with high degree AV block, heart failure with reduced ejection fraction (HFrEF) and NYHA I-IV functional class in order to reduce morbidity (1A evidence, Table 1-5).[11] Patients with AF were included in this guidance.

Table 1-5: Summary of 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure Relating to CRT and RV Pacing in Patients with High Degree AV Block

ESC Recommendation	Class	Level
CRT is recommended over RV pacing for patients in sinus rhythm or AF, with HFrEF of any NYHA functional class, who have an indication for ventricular pacing and high degree AV block, in order to reduce morbidity.	**I**	**A**
CRT is recommended over RV pacing in patients with HFrEF who require pacing with a high degree of AV block.	**I**	**A**
Pacing modes that avoid inducing or worsening ventricular dyssynchrony should be considered for patients with HFrEF who require ventricular pacing without high degree AV block.	**IIa**	**C**

Adapted from ESC 2016 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [11]

Abbreviations

ESC = European Society of Cardiology, CRT = Cardiac Resynchronisation Therapy, HFrEF = Heart failure with reduced ejection fraction, NYHA = New York Heart Association, AV = Atrioventricular, RV = Right ventricular

1.2.7 Conclusions on chronic RV pacing in the heart failure population

The role of CRT pacing in patients with AV block and impaired LV systolic function remains an important consideration. The BLOCK HF trial demonstrated better outcomes with CRT pacing over RV pacing in patients with LVSD and AV block in patients expected to have a high RV pacing burden. However, BLOCK HF failed to demonstrate any mortality benefit. The preliminary results of the European-based BioPace trial have not

confirmed the same statistically significant benefit, although we are still awaiting the full results to be published. In the interim, CRT pacing seems to have a beneficial effect on LV reverse remodelling, systolic function and clinical outcomes in patients with NYHA functional class I-III heart failure, moderate to severe LVSD and AV block compared to RV pacing. However, it is less clear whether there is a similar benefit from CRT in patients with a high percentage of RV pacing who have normal or mild LVSD in the treatment of AV block.

1.3 Evaluating CRT response

CRT has been in clinical use now for over 20 years and is an excellent treatment for certain groups of patients with heart failure. However, a significant proportion of patients still fail to improve,[96] which has unfortunately remained static despite significant advances in technique and technology. CRT non-response therefore remains a significant problem in the treatment of heart failure[5,97,98] and its prevalence is summarised in Figure 1-4.

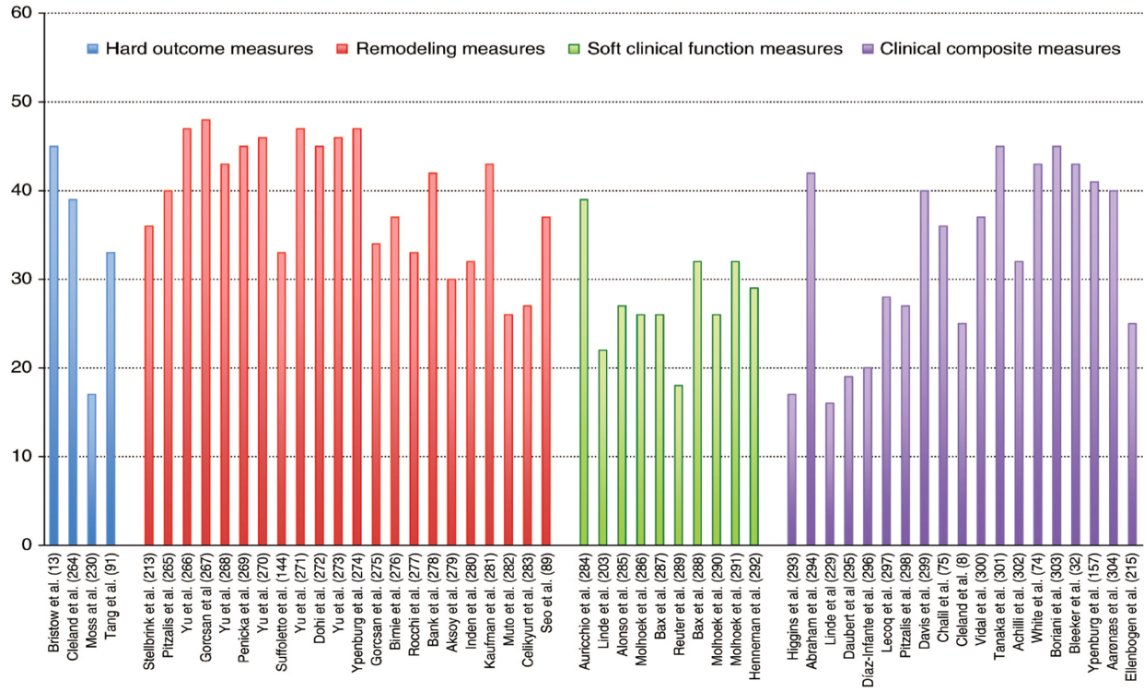

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Figure 1-4: Prevalence of CRT non-response

'Non-response (y axis, %) amongst clinical studies (x axis, first author, year). Hard outcome measures (blue): mortality and heart failure hospitalisation. Remodelling measures (red): use of reductions in LVESV on echocardiography. Soft clinical function measures (green): 6-minute walking distance and clinical scoring questionnaires. Clinical composite measures (purple): for example, Packer's clinical scoring system.'[96]

There also remains a lack of consensus on how best to define and measure CRT response,[99] and several approaches have been used including both subjective and objective metrics:

- Subjective – patient quality of life questionnaires.[8]
- Mixed subjective and objective – clinical composite score
- Objective - echocardiographic remodelling,[100] including reduction in LV end systolic volume (LVESV) by >15% compared with baseline.
- Objective - VO_2 max using cardiopulmonary exercise testing.
- Objective - Heart failure hospitalization, all-cause mortality, cardiovascular mortality and the composite endpoint, major adverse cardiovascular events (MACE).

Approximately 30-50% of patients undergoing CRT fail to derive any benefit, depending on heart failure aetiology and the metric used to evaluate response.[5] In addition, over 40% of patients undergoing CRT show no objective evidence of ventricular reverse remodelling.[5,97,101–103] Poor patient selection, suboptimal LV lead positioning and insufficient delivery of CRT are important causes of CRT non-response.[104–106] In addition, disease aetiology[107–113]; pattern of dyssynchrony [112–115]; patient selection[5,97,116]; site of LV stimulation [6,103,117–122]; and device programming[102,103,123,124] have been identified as predisposing factors of CRT non-response. Figure 1-5 summarises some of the important causes of CRT non-response. LV scar may also reduce the reverse remodelling potential with CRT and patients with ischaemic cardiomyopathy show less improvement in LV ejection fraction (LVEF) than those with dilated cardiomyopathy.[5] Suboptimal LV lead position has been reported to occur in 21% of cases and may be lead to poor patient outcomes.[103,125,126] The posterolateral and lateral coronary veins have been shown to

best correlate with later electrical activation and improvement in echocardiographic volumetric measures compared to septal or anterior LV lead positions.[6,118,120,121,127,128] However, due to variations in coronary venous anatomy, using coronary veins to assess optimal LV lead placement may not be ideal.[103,122] Furthermore, LV scar location and its relationship to electromechanical delay also need to be considered.[103,122] Patterns of electrical activation also differ between ischaemic and non-ischaemic cardiomyopathies and therefore, heart failure aetiology may play a role in optimal LV lead positioning.[129]

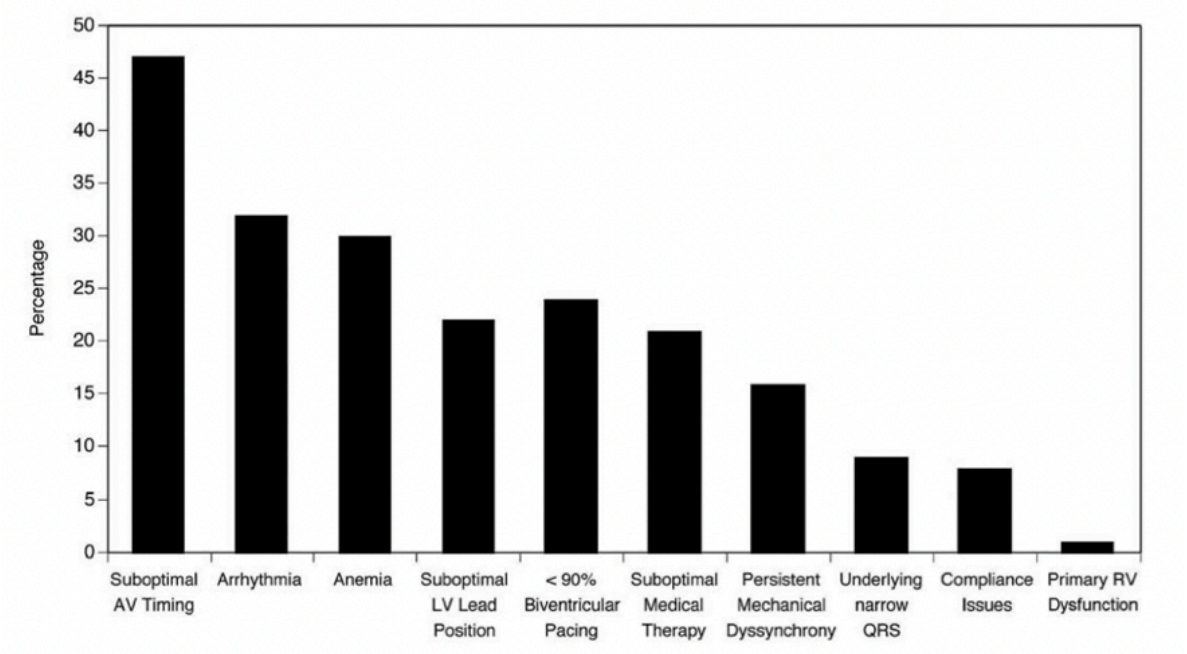

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Figure 1-5: Causes of CRT non response in a group of 75 patients.

Left ventricular reverse remodelling has previously been shown to be a robust predictor of cardiovascular clinical outcomes in numerous heart failure landmark trials for the use of ACEI and beta-blockers.[1,130,131] Additionally, mortality reduction is predicted by LV reverse remodelling rather than clinical improvement measures and hence echocardiographic volumetric assessments are often used in studies evaluating

techniques to improve CRT response.[132] However, quantifying LV reverse remodelling using echocardiographic volumetric assessments has a sensitivity and specificity of approximately 70% which implies that up to a third are incorrectly classified.[133] However, these limitations have been considered acceptable and have been adopted as the benchmark metric for evaluating volumetric response in many important CRT trials.[4,134–136]

1.4 Strategies to improve CRT delivery

In the modern era of advancing medical technology and imaging, it is important to ensure that the basics are still considered when assessing patients for CRT and later in ensuring maximum CRT capability is achieved once implanted with a CRT device. Ensuring patients meet CRT guideline inclusion criteria[11,137] is important, although there will be cases where clinicians need to deviate from such guidelines when treating patients with heart failure. Notably, the EchoCRT trial demonstrated that patients with a relatively narrow QRS duration <130ms on surface electrocardiogram (ECG), despite having objective evidence of mechanical dyssynchrony on 2D-echocardiography, had significantly higher rates of all-cause mortality in those with CRT turned on compared to those who had CRT turned off.[35,138] In addition, successful deployment of the LV lead to a stable and lateral position with a good capture threshold and absence of phrenic nerve stimulation is of paramount importance for all CRT procedures. Occasionally, complex coronary venous anatomy and/or extensive scar dictate transvenous epicardial LV lead positioning and pre-procedural cardiac computed tomography (CT) or magnetic resonance imaging (MRI) may help plan for such technical challenges and potentially inform a different CRT delivery strategy e.g. surgical epicardial LV lead placement, His bundle pacing or endocardial LV lead implantation using the wireless stimulation endocardially (WiSE) CRT system (EBR systems, Sunnyvale, CA, USA). These same techniques may also be considered for patients that have not responded to conventional CRT. Follow-up of CRT patients is equally important to optimise heart failure pharmacotherapy as well CRT. Ensuring patients have any causes of suboptimal biventricular pacing (<95%) e.g. ventricular ectopy or atrial tachyarrhythmias addressed is paramount. Echo and/or ECG guided optimisation of atrioventricular and/or

ventriculo-ventricular intervals after CRT implantation remains uncertain but may be considered when patients have a poor response to CRT[11,139,140] Minimising shocks from CRT-defibrillators (CRT-Ds) as well optimizing battery longevity are other important areas to address during CRT follow-up assessments.

There are also a number of advanced strategies including multimodality imaging, multisite pacing, multipoint pacing, acute haemodynamics, electrical parameters and mapping that have been trialled to optimise LV lead delivery and allow operators to place transvenous LV leads in locations that aim to optimise mechanical and electrical synchrony and ultimately CRT response.[141]

This thesis will now focus on the potential roles of image guidance and multipoint LV pacing in targeting areas of dyssynchrony and avoiding LV scar.

1.4.1 The rationale for targeting dyssynchrony

The basis for targeting dyssynchrony lies in the electrical disruption and electrical slowing of myocardial conduction that occurs in heart failure, leading to interventricular delay typically observed as LBBB on a 12-lead surface ECG.[142] This frequently results in poor interventricular coordination and inefficient contraction culminating in reduced cardiac output[143] and progressive left ventricular dilatation.[50] Re-establishing electrical and mechanical synchronous contraction is thought to be the mechanism by which CRT works.[29] Whilst QRS prolongation on the 12-lead surface ECG reflects electrical dyssynchrony, it does not always parallel mechanical dyssynchrony.[112,144] Furthermore,

it is possible to have mechanical dyssynchrony both with a normal QRS duration <120ms and preserved LV systolic function.[145]

1.4.2 The rational for avoiding left ventricular scar

It is widely recognised that patients with extensive LV scar have less improvement in LV systolic function with CRT, however, this is also true when they are treated with pharmacotherapy and does not reliably predict less clinical benefit.[11,146] Moreover, there is little evidence that they obtain less prognostic benefit from CRT despite having an intrinsically worse prognosis.[11,33]

High lead pacing thresholds occur in scarred myocardium and hence should be avoided where possible to preserve battery life and reduce the chance of phrenic nerve stimulation.[11,125,126] There is also a concern that pacing in scarred regions of the LV may promote ventricular tachyarrhythmias and worsen prognosis,[147–150] although this may be improved with catheter ablation.[151] It is therefore this group of patients that are likely to gain the most from an image guided approach that may help avoid LV scar and place the LV lead in the region of latest mechanical activation outside of scar.

1.5 Image guidance for CRT

Multimodality cardiac imaging has often been used to identify patients most likely to respond to CRT.[112,113,152] More recently, pre-procedural LV target selection as well as real-time image overlay guidance have been explored in order to help operators target areas of latest mechanical and/or electrical activation i.e. areas of dyssynchrony and avoid regions of LV scar in order to achieve the most optimal LV lead position for the delivery of CRT.[153–156]

1.5.1 Echocardiography to guide LV lead implantation

Two-dimensional echocardiography has been integral in selecting suitable patients for CRT as well as monitoring their progress. It has also been used to predict which patients are most likely to respond CRT by evaluating dyssynchrony. Numerous techniques and metrics have been the focus of research studies for the last 20 years including 2D echocardiography, 3D echocardiography, tissue doppler imaging and speckle tracking.[104,112,113,152] Speckle tracking echocardiography has been used in two important image guided trials; The TARGET[125] and STARTER[157] trials. These single centre randomised controlled studies both identified target segments based on speckle tracking indices to identify areas of latest mechanical activation for LV lead delivery. Both studies concluded that speckle tracking image guidance leads to significantly improved CRT response outcomes compared to standard CRT implantation. However, both studies most likely excluded LV scarred segments on the basis of wall thickness and/or low amplitude strain curves and therefore the final pacing target was frequently

remote from LV scar. It is therefore plausible that targeting late mechanical dyssynchrony may represent a surrogate for avoiding myocardial scar.

3D echocardiography potentially allows for a more comprehensive and true representative assessment of ventricular dyssynchrony and can account for out of plane movement of myocardial segments throughout ventricular systole and diastole. However, despite advances in both 2D and 3D echocardiography, a distinct and reproducible predictor of dyssynchrony and CRT response has not yet been identified which may be related to inter-operator variability and suboptimal echocardiographic windows for accurate dyssynchrony quantification. Finally, echocardiography is only able to infer scarred regions of the LV using certain criteria including myocardial wall thinning (<6mm) on 2D echocardiography[158] and absence of contractile reserve during dobutamine stress echocardiography[159] Whilst these surrogate markers for LV scar may help predict CRT response, echocardiography cannot provide direct visualisation and quantification of LV scar tissue that is possible with myocardial perfusion imaging, cardiac magnetic resonance (CMR), and increasingly with cardiac CT.

1.5.2 Myocardial perfusion imaging to guide LV lead implantation

Faucheir et al. (2002) described the early assessment of LV contraction timing using phase analysis.[160] More recently, the integration of single photon emission CT with nuclear perfusion imaging has allowed 3D assessment of regional LV motion.[161,162] Myocardial perfusion imaging has been shown to reliably assess regional dyssynchrony.[163] It also offers robust myocardial substrate imaging, especially in terms of LV function and scar burden evaluation, the latter of which has been shown to

correlate with less LV reverse remodelling,[164] in keeping with that seen with late gadolinium enhancement (LGE) imaging with CMR.[165] Furthermore, myocardial perfusion has been beneficial in predicting CRT response,[161,162,166] however, high radiation doses are likely to limit its widespread use, including with regards to image guidance for CRT compared with other techniques.

1.5.3 Cardiac magnetic resonance to guide LV lead implantation

Cardiac magnetic resonance is an advanced cross-sectional imaging modality that offers superior spatial resolution, accurate endocardial border definition and suffers less from operator/analyser variability compared to echocardiography.[167] It's temporal resolution is acceptable but inferior to echocardiography. Excellent anatomical and functional images are readily achievable in the majority of patients using steady state free precession (SSFP) sequences. Functional imaging data can be readily used to quantify dyssynchrony using tissue tracking algorithms similar to those used in echocardiography and calculate both regional and global dyssynchrony scores.

Simonetti et al (2001)[168] described the early use of CMR to detect ventricular scar using LGE sequences which has evolved into the current gold standard for assessing myocardial fibrosis (scar).[169,170] LV scar burden and location relative to LV lead placement are important factors in determining CRT response.[165,171–173] reported that higher scar burdens were associated with inferior LV reverse remodelling rates and either no improvement in LVESV or progressive dilatation of the LV cavity was observed in patients with a very high scar burden. LV pacing remote to scar identified on CMR has been shown to result in more favourable CRT response rates,[173] which suggests that

using real-time CMR overlay guidance to locate and avoid scar may be beneficial.[155] It is important to note that LV leads are often empirically deployed in a lateral or posterolateral vein as these coronary veins typically subtend to myocardial segments that most often correspond to areas of late electrical activation. However, pacing over posterolateral scar is associated with poor response to CRT[173] and therefore implies an image guided approach to avoid LV scar may be important and more sensible than empirical LV lead implantation.

Left ventricular mid-wall fibrosis seen in patients with non-ischaemic cardiomyopathy also results in suboptimal outcomes with CRT, albeit to a lesser extent than that seen with patients with subendocardial or transmural scar.[174] Therefore, dedicated real-time image guidance studies for patients with non-ischaemic scar may be consider in the future.

However, CMR has its limitations as an image guidance tool. Approximately 28% of patients undergoing CRT have a pre-existing pacing or ICD system and are often unsuitable for CMR.[96] Whilst we are starting to MRI patients with non-MRI conditional pacing systems, this is not always possible due to abandoned leads and is not entirely risk free, particularly in patients that are pacing dependent. Furthermore, patients with heart failure awaiting CRT often find CMR scans challenging due to long breath holds and a prolonged period of 30-45 minutes supine which often affects image quality through respiratory motion artefact. There is also a risk of nephrogenic systemic fibrosis with gadolinium contrast agents used in CMR scar imaging, particularly in patients with renal impairment which is common in the heart failure population. Additionally, image degradation from lead artefact may impede the use of using CMR images for

dyssynchrony analysis. Cardiac CT has shown excellent promise in addressing these limitations of CMR in imaging patients with pre-existing CIEDs.

1.5.4 Cardiac Computed Tomography to guide LV lead implantation

Cardiac CT has the potential to guide LV lead placement.[153,154,156,175] Rapid acquisition of isotropic 3-dimensional whole heart data sets with submillimetre spatial resolution allows accurate assessment of coronary venous anatomy[175,176] as well as non-invasive assessment of regional and global LV systolic function.[175,177] Additionally, cardiac CT may be used to evaluate LV dyssynchrony and areas of LMA,[175,178] and has the potential to detect regional hypoperfusion/myocardial scar,[179] albeit with varying results and no clearly standardized imaging protocols to reliably identify late iodine enhancement.[180] Identification of LV scar through first pass hypoperfusion as well as late iodine enhancement which has similar pharmacokinetics as Gadolinium used in CMR have been investigated. Gerber et al. (2006) showed that early hypoperfusion may however reflect acute myocardial injury from microvascular obstruction whereas late iodine enhancement may reflect chronic scar formation/infarction in a porcine model.[181] In the absence of regional hypokinesis or akinesis, hypoperfusion may not be specific to myocardial injury[182] and late iodine contrast uptake into the myocardium may also reflect hypoperfusion without necessarily infarction.[183] Modern dual energy CT scanners have the potential to allow better and more reliable scar assessment through late iodine enhancement by using two simultaneous sources of energy to identify more subtle changes in tissue characterisation.[179]

Cardiac CT has a few limitations, although through rapid advancements in CT technology these are gradually becoming less problematic. Hard-beam artefact from metallic objects including mechanical heart valves and pacing wires can lead to image degradation. However, there are now excellent algorithms that are able to limit this effect[184–186] and as such measuring LV dyssynchrony remains possible in most patients with pre-existing right atrial and RV pacing leads.[175] In addition, whilst the temporal resolution of CT has significantly improved (up to 66ms with current dual source scanners) this remains inferior to echocardiography (20ms) and CMR (35-50ms obtained over multiple heart beats) and therefore cardiac CT may be less sensitive to subtle regional motion changes. There is also an ionizing radiation dose to factor in when using CT, however the plethora of detailed cardiac information obtainable often outweighs the negative impact of using ionizing radiation in the heart failure population, particularly in patients unable to undergo a CMR scan. Furthermore, radiation doses have dramatically fallen with modern CT scanners making ionizing radiation less concerning than with early cardiac CT imaging. Nonetheless, a radiation assessment should always be taken into account when considering using CT. Additionally, use of cardiac CT may not be feasible in all patients because of significant renal impairment and given the small risks of ionising radiation this may not be an appropriate imaging modality for all groups of patients. An in-depth feasibility analysis of using cardiac CT for real-time image overlay guided LV lead implantation is covered in Chapter 2.

1.6 Left ventricular multisite pacing

An alternative strategy to improve CRT response rates has focused on increasing the number of LV stimulation sites using multisite pacing which may improve CRT response by increasing the probability of pacing at an optimal site. In addition, by capturing more LV myocardium, a greater number of sites may provide faster and more physiological LV activation. Multisite LV pacing has the potential advantage over multipoint pacing using a quadripolar lead in that it allows a theoretical larger separation of the two LV electrodes. Multisite LV pacing with two LV leads may allow simultaneous recruitment of a larger volume of viable LV myocardium compared to single or multipoint LV pacing and therefore be more effective in reversing dyssynchrony.[187] Stimulating the LV using multisite LV pacing may capture the myocardium around areas of scar more effectively resulting in an improvement in CRT response. Previous studies have shown the feasibility of multisite LV pacing and it has been shown to improve clinical parameters and ventricular reverse remodelling compared to biventricular pacing.[98,187–189]

Whilst experimental data has suggested that patients with a high probability of a good response to BiV pacing (i.e. patients with a broad LBBB) are unlikely to obtain incremental benefit from implanting an additional LV pacing lead, there remains a clinical need to try to improve response rates in patients with less clear indications for BiV pacing and multisite LV pacing offers a possible way for this to be achieved.[187,190,191]

The STRIVE HF (Standard care versus TRIVEntricular pacing in Heart Failure) trial is currently underway to examine whether LV multisite pacing (two LV leads and one RV lead) in patients with LBBB with a moderately prolonged QRS duration of 120-150 ms is

feasible and superior in terms of the proportion of patients who successfully reverse remodel compared to standard BiV pacing. An in-depth interim review and analysis of the STRIVE HF trial is covered in Chapter 3. In addition, a detailed review of previous multisite trials is explored in the discussion section 3.4.

1.7 Implantable cardioverter-defibrillators in the heart failure population

A large proportion of deaths among patients with heart failure occur suddenly and are frequently due to electrical disturbances.[11] Importantly, sudden death often occurs in patients with milder heart failure symptoms and many are due to ventricular tachyarrhythmias, bradyarrhythmias and asystole. Whilst certain antiarrhythmic agents may reduce the burden of tachyarrhythmias and sudden death, major trials have failed to demonstrate a reduction in overall mortality and may even increase it.[11] Importantly, ICDs have been shown to be effective in preventing bradycardia and correcting potentially fatal VAs.[11] ICDs have been shown to reduce mortality from VAs but are associated with complications including inappropriate shocks, lead/device malfunction and infection.[61] Mortality rates are higher in patients receiving ICD shock therapy[192,193] which may lead to heart failure progression.[194]

1.7.1 Improving ICD risk stratification

The vast majority of sudden cardiac deaths are due to malignant ventricular tachyarrhythmias and are responsible for the deaths of over 70,000 people in the UK and approximately 300,000 people in the United States each year.[195,196]

Pharmacotherapy for the prevention of sudden cardiac death has been largely negative with only beta-blockers exhibiting benefit in randomised clinical trials.[197] The SWORD[198] and CAST[199] trials were both terminated prematurely following an interim analysis that

revealed an excess of deaths in patients randomised to receive antiarrhythmic therapy compared to placebo. Additionally, the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial showed that amiodarone was inferior to ICD therapy and equivalent to placebo in preventing deaths for patients with heart failure.[200]

Contrastingly, electrical therapy in the form of direct current cardioversion remains very effective in the treatment of ventricular tachyarrhythmias by restoring a stable heart rhythm. The development of ICDs in the last 30 years was a significant landmark in modern medicine.[61,201–203] However, whilst ICDs reduce mortality from VAs, they are associated with complications including infection, lead malfunction and inappropriate shocks.[61,204–206] Notably, mortality rates are higher in patients receiving ICD shock therapy[192,193] and may lead to heart failure progression.[194] A recent large meta-analysis including almost 200,000 patients demonstrated mortality was greater for appropriate compared to inappropriate shock therapy but both were associated with reduced survival with multiple shocks predicting worse outcomes.[193,207] Furthermore, appropriate ICD therapy only occurs in one third of patients implanted with an ICD indicating better risk stratification of VA is needed.[208] Identifying VAs may also play an important role in identifying patients who may benefit from prophylactic ventricular tachycardia (VT) ablation.

Despite considerable research into potential indicators, risk stratification of arrhythmic sudden cardiac death remains complex.[209] This is compounded by the fact that approximately 50% of sudden cardiac deaths occur in individuals living with undiagnosed ischaemic heart disease.[210] This has led to a significant drive in improving public health through the use of cardiac risk scores with a focus on improving patient

education and the modification of risk factors associated with the development of ischaemic heart disease.[211,212]

Over the last 20 years, there has also been a vast array of research into identifying suitable metrics to predict fatal arrhythmias. Multiple information from historical factors, biomarkers, autonomic parameters (heart rate variability, baroreflex sensitivity), surface ECG abnormalities (QT variability, T-wave alternans, T-wave oscillations), invasive electrophysiology (EP) studies, intracardiac electrograms, provocation testing and cardiac imaging (LVEF, ventricular scar assessment) have proven important although none offer 100% sensitivity.[213,214]

Current guidelines base risk stratification of patients at risk of malignant VAs using transthoracic echocardiographic LVEF $\leq$35% as a surrogate for severely impaired cardiac function in order to guide which patients should be considered for an ICD in the primary prevention of arrhythmic sudden death.[61,200,201] However, LVEF $\leq$35% as a sole metric for ICD risk stratification appears to be suboptimal given patients with normal or mild-moderate LV systolic impairment still have either aborted or fatal VAs. In addition, the recent Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) has demonstrated the need for additional risk stratification metrics.[209] Moving forwards, it is likely that formal risk stratification tools will need to incorporate multiple modalities as it is unlikely any single measure will have sufficient discrimination to be used in isolation and individual risk can markedly change over time suggesting static assessment is insufficient for accurate long-term risk stratification.

Non-invasive LV scar analysis using CMR and LGE sequences is one modality that has shown promise in the prediction of VAs and has potential as an ICD risk stratification metric in the primary prevention of arrhythmic sudden cardiac death. This thesis will therefore focus on the quantification of scar heterogeneity using cardiac MRI texture analysis to calculate entropy as a potential ICD risk stratification tool in chapters 4 and 5.

1.8 Summary and hypotheses

Cardiac resynchronisation therapy is an effective treatment for certain patients with heart failure. However, a significant proportion of patients fail to respond to CRT and there is potential to improve CIED outcomes through improving CRT response rates. There are several advanced strategies that have been trialled to improve LV lead delivery by allowing operators to place transvenous LV leads in locations that aim to optimise mechanical and electrical synchrony with the aim of improving CRT response.

Initially, this thesis explores two distinct and important strategies to improve CRT response by targeting areas of dyssynchrony and avoiding LV scar tissue:

1. Image guidance using cardiac CT in patients undergoing an LV lead upgrade to CRT procedure. Chapter 2 addresses the hypothesis that using cardiac CT will lead to an improvement in CRT response rates and patient outcomes.
2. Multisite LV pacing in patients undergoing *de novo* CRT-D implantation. Chapter 3 addresses the hypothesis that multisite LV pacing will lead to an improvement in CRT response rates and patient outcomes.

ICD risk stratification represents another important area to target in order to improve CIED outcomes. A large proportion of deaths among patients with heart failure occur suddenly and are frequently due to electrical disturbances. However, ICD risk stratification is complex and currently sole use of LVEF $\leq$35% is insufficient.

Finally, this thesis explores quantifying scar heterogeneity using cardiac MRI texture analysis to calculate entropy from LGE imaging as a potential ICD risk stratification tool. Specifically:

1. Scar heterogeneity, quantified by mean entropy, to predict appropriate ICD therapy. Chapter 4 addresses the hypothesis that high mean entropy, calculated from CMR-TA, will predict appropriate ICD therapy in patients undergoing *de novo* ICD implantation.
2. Scar heterogeneity, quantified by mean entropy, to predict anti-tachycardia pacing (ATP) failure. Chapter 5 addresses the hypothesis that high mean entropy, calculated from CMR-TA, will be higher in patients with failed ATP compared to those receiving successful ATP.

Chapter 2: Real-time cardiac CT image overlay to guide optimal left ventricular lead implantation for CRT upgrades

2.1 Introduction

Patients with moderate to severe LV systolic dysfunction and a pre-existing pacing or ICD system may benefit from an upgrade to CRT for pacing induced cardiomyopathy as well as other aetiologies.[37,88] Non-response to CRT occurs in up to 30-50% of patients depending on heart failure aetiology and whether CRT response is assessed as an improvement in patient symptoms or the percentage of reverse remodelling using echocardiography volume and LVEF quantification. Suboptimal LV lead positioning is an important cause of CRT non-response and most likely occurs because of LV lead placement in myocardial scar with persistent dyssynchrony.[215,216] Cardiac magnetic resonance imaging can guide LV lead placement by targeting LMA and avoiding LV scar,[155,217] however, 28% of patients undergoing CRT have a pre-existing pacing or ICD system and may be unsuitable for CMR.[96] Imaging patients with non-MRI conditional pacing systems is not always possible due to abandoned leads and is not entirely risk free, particularly in patients that are pacing dependent. Furthermore, patients with heart failure often find CMR scans challenging due to long breath holds and a prolonged period 30-45 minutes supine which often affects image quality through respiratory motion artefact. Additionally, CMR image degradation from lead artefact frequently impedes the use of using CMR images for dyssynchrony analysis in our experience.

Cardiac CT has the potential to guide LV lead placement.[153,154,156,175] Rapid acquisition of isotropic 3-dimensional whole heart data sets with submillimetre spatial resolution allows accurate assessment of coronary venous anatomy[175,176] as well as non-invasive assessment of regional and global LV systolic function.[175,177] Additionally, cardiac CT may be used to evaluate LV dyssynchrony and areas of LMA,[175,178] and has the potential to detect regional hypoperfusion/myocardial scar,[179] albeit with varying results and no clearly standardized imaging protocols to reliably identify late iodine enhancement.[180]

We have previously shown that offline pre-procedural cardiac CT dyssynchrony analysis produces functional data sets with sufficient temporal resolution to differentiate the region of LMA in a separate cohort of 18 patients and that CT target selection correlates well with an acute haemodynamic response (AHR) >10%.[175] This study sought to test the feasibility of a purpose-built, integrated software platform to process, analyse and overlay CT data in real-time within a cardiac catheter laboratory to guide LV lead implantation.

2.2 Methods

Between September 2017 and August 2019, 18 patients undergoing an LV lead upgrade to CRT procedure from either a pre-existing pacemaker or ICD were prospectively enrolled. All patients provided written informed consent. The study protocol was approved by the West Midlands Research Ethics Committee (Research Ethics Committee approval number 14/WM/1069) and conducted in accordance with the Declaration of Helsinki.

2.2.1 Recruitment and follow-up

Consecutive patients with heart failure and an LVEF <45% undergoing an LV lead upgrade to CRT from either a pre-existing pacemaker or ICD were screened for their eligibility. Patients of any gender, at least 18 years of age could participate in the study if they were able and willing to comply with all study requirements and provide informed consent. Patients were required to be stable on optimal heart failure pharmacotherapy for at least 3 months prior to enrolment. All aetiologies of heart failure were eligible for this feasibility study and patients with sinus rhythm or AF were included. Patients were ineligible if they had insufficient capacity to consent to the study, a life expectancy of less than a year, an eGFR of less than 30mL/min/1.73m^2, previous iodine contrast allergy or any contraindication to CRT or transvenous LV lead implantation via the coronary sinus. In addition, patients were not eligible if they had any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the

participant's ability to participate in the study. Female participants who were pregnant, lactating or planning pregnancy during the course of the study were not eligible for enrolment.

All study participants underwent a dedicated cardiac CT research protocol prior to the CRT upgrade procedure. Eligible patients underwent the following tests at baseline and six-month follow-up visits: NYHA functional class assessment; physical examination; 12-lead resting ECG; 2D TTE including Simpson's biplane assessment for left-ventricular end-diastolic volume (LVEDV), LVESV and LVEF; MLWHFQ score; and 6MWT. In addition, patients underwent a full CRT device and pacing check at the six-month follow-up visit.

2.2.2 Pre-procedural Cardiac CT dyssynchrony imaging protocol

Cardiac CT examinations were performed using a 3rd generation dual source scanner (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). Intravenous metoprolol was used to achieve a heart rate of <65 beats/min in sinus rhythm and <100 beats/min in AF. A topogram was scanned as localizer and for the automatic exposure control. Following an injection of 120 mL iodinated contrast material (Omnipaque 350 mg/ml iodine, GE Healthcare, Princeton, NJ) at 5 mL/s via the antecubital vein, a retrospective ECG gated cardiac computed tomography angiogram (CTA) was performed with reference dose settings of 100 kV and 288 mAs/rot. Contrast monitoring triggered the scan with 14 s delay after reaching 100 HU (at 100kV) in the descending aorta. The cardiac CT scan provided the full cardiac function for motion analysis over the entire cardiac cycle (0-100% every 5%) and coronary venous anatomy imaging for identifying a target vein in the target segment.

2.2.3 Pre-procedural cardiac CT scar imaging and dyssynchrony analysis

For the first 8 patients (protocol A), at 7 minutes after contrast injection completion, patients underwent end-systolic prospectively ECG triggered late enhancement scanning with a dual energy scan for patients in sinus rhythm with a heart rate <65 beats/min. The dual energy scan was performed at 90/Sn150 kV with 165 and 127 reference mAs respectively with a full 250ms reconstruction. A single energy shuttle mode (dynamic scan) was used for patients in AF and/or a heart rate >65 beats/min. The scanner alternates rapidly between two table positions and acquires prospectively ECG-triggered axial images in these two positions for 15 seconds. The trigger was set end-systole at 250ms. The shuttle mode was scanned for 15 seconds (4-5 cycles) at 80 kV/300 mAs reference dose settings. For the last 10 patients (protocol B), at 12 minutes and 30 seconds after contrast injection completion, all patients underwent shuttle mode dynamic scanning as described above, regardless of cardiac rhythm or heart rate. The reference dose was also increased by 30% to ref kV 80 and ref mAs 390.

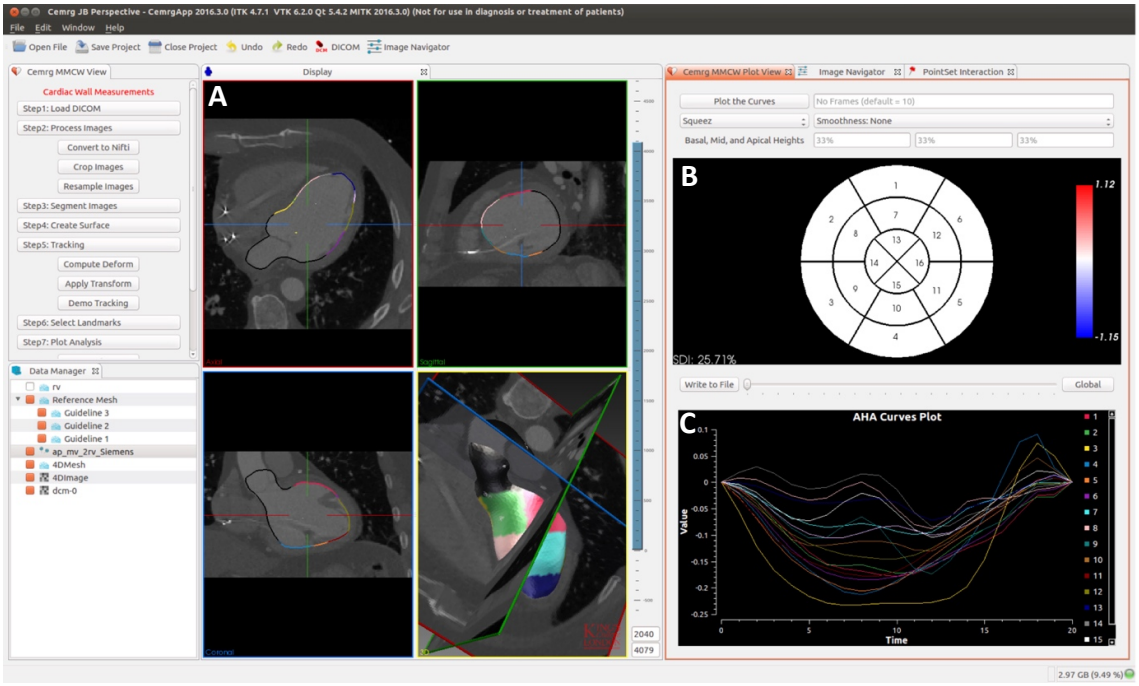


Figure 2-1: Cardiac CT dyssynchrony analysis

Our Cardiac CT Dyssynchrony analysis platform is based on the open-source software medical imaging interaction toolkit (MITK) and provides a simple stepwise approach for tracking wall motion from cardiac CT datasets.

A) Interactive image rendering for visualising 3D images and surface meshes

B) 16-segment bullseye plot for visualisation of myocardial strain at every phase throughout the cardiac cycle.

C) Individual volume (Y-axis) over time (X-axis) strain curves for each of the 16 endocardial segments. The apical cap is not included as a segment.

Our comprehensive cardiac CT dyssynchrony assessment methodologies are adapted from Behar et al (2017).[175] In brief, LV dyssynchrony was calculated using an opensource clinician-focused platform (Figure 2-1) by applying an image registration warping field to a triangulated mesh of the LV endocardium from the retrospective ECG gated cardiac CT angiogram (0-100% phase, incrementing every 5%). Two registration methods were optimised to track endocardial wall motion. Both methods required a single semi-

automated segmentation of the left ventricle cavity at end-diastolic phase. The motion was characterised by the circumferential and longitudinal strains as well as local area change throughout the cardiac cycle. The derived motion was validated against manually annotated anatomical landmarks and the calculation of strains were verified using idealised problems. Figure 2-2 shows annotated motion tracking results in further detail.

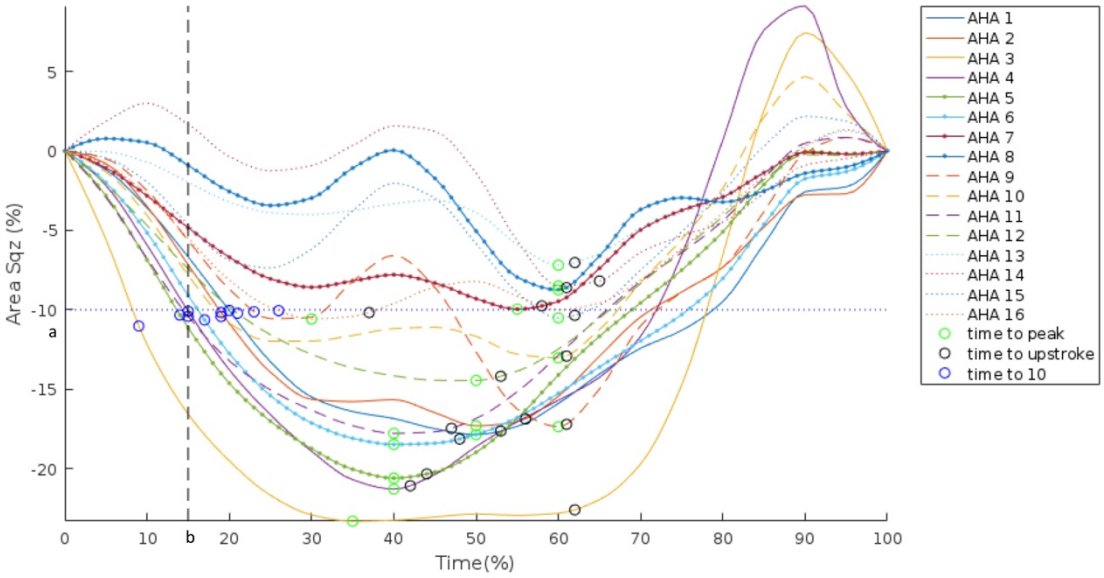


Figure 2-2: Annotated dyssynchrony plots of volume change (Y-axis) over time (X-axis)

[a] Time to 10% represents the time taken for the area of each AHA segment to reduce in size to 90%.

[b] Retrospective analysis of historical cases showed that a 15% threshold of time to 10% could be used to distinguish between LV lead pacing locations which correspond with response and non-response to CRT.

Late iodine enhancement images were reconstructed with a slice thickness of 2mm and an increment of 1mm with a medium smooth kernel (Qr36) and iterative correction of iodine beam hardening. The time points of the dynamic scans were averaged after non-rigid registration. The resulting average volume was then loaded into a DICOM viewer and displayed in cardiac planes and qualitatively evaluated in apical, mid, and basal

views of the short axis orientation in a narrow window. For comparison, a systolic phase of the retrospective cardiac CTA was loaded in synchronized orientation.

2.2.4 Image overlay using the Guide CRT platform prototype

Our image overlay methods using the Guide CRT platform (Siemens Healthineers, Forchheim, Germany) for cardiac MRI have been previously described.[175,218–221] In brief, the Guide CRT platform is a custom-built software prototype developed by the Department of Imaging Sciences & Biomedical Engineering and Siemens Healthineers and is integrated into our Artis Q biplane Angiography system (Siemens Magnetom Artis Combi Suite, Siemens Healthcare GmbH, Erlangen, Germany). The Guide CRT platform was installed on a dedicated prototype workstation connected to the biplane fluoroscopic system. Rapid, automatic data processing enables information to be extracted from either cardiac CT or MRI.

The Guide CRT platform incorporates an automatic protocol for slice registration and LV segmentation. Additional features not used in this study include semiautomatic LV scar segmentation, transmurality and overall scar burden (%). Manual adjustment of the segmentation process is possible and final verification by the clinical operator is required to confirm the registration process.

2.2.5 Real-time CT guided CRT workflow

The ECG gated cardiac CT angiography images (0-100% phase, incrementing every 5%) together with the CT dyssynchrony values (plots) were uploaded to the Guide CRT platform and processed as follows (Figure 2-3):

1. Automatic segmentation of the LV epicardium and endocardium with manual adjustment of the segmentation where required to create a 3D mesh of the LV (Figure 2-3A).
2. Semi-automatic segmentation of the coronary sinus was performed by adding intermittent markers along the coronary sinus and coronary veins (Figure 2-3B).
3. Integration of the CT derived dyssynchrony values (plots) acquired as described above (Figure 2-3C).
4. Following review of the regional dyssynchrony curves to identify the latest mechanically activating segments (latest time to peak contraction), the optimal target myocardial segment(s) for LV delivery were selected on a corresponding 16-segment American Heart Association (AHA) bull's-eye plot (Figure 2-3D) according to the target segment selection protocol outlined in detail below. LV scar (whether inferred or directly visualised on CT) was avoided where possible when choosing the target LMA segment. Scar burden and transmurality were not incorporated into the workflow due to inconsistencies of identifying scar on CT.
5. Fusion of the target AHA segment with the coronary sinus segmentation was performed to identify a target vein subtending the target segment (Figure 2-3E).

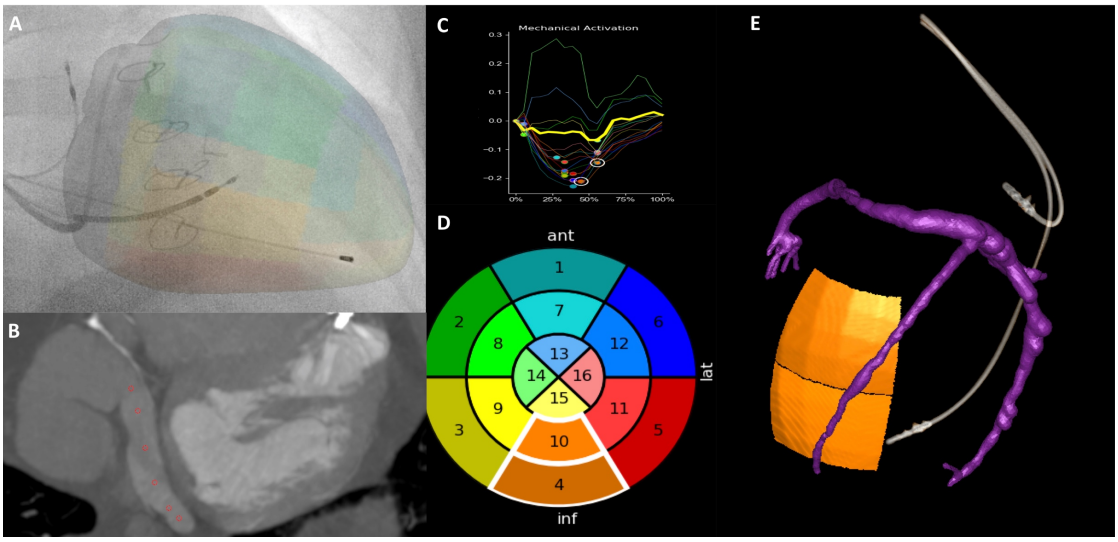


Figure 2-3: Pre-implant CT Guided CRT workflow

A) Automatic segmentation generates a 3D mesh of the left ventricle.

B) Semi-automatic segmentation of the coronary venous anatomy using 3D markers (red circles) generates a 3D reconstruction of the coronary sinus and tributary veins.

C) Integration of the CT-derived dyssynchrony plots allows for choosing the latest mechanically activating segment.

D) Target selection is then made on the AHA 16 segment Bull's eye plot using the dyssynchrony plots.

E) 3D fusion of the coronary venous anatomy in relation to the chosen target segment(s) is performed showing a target vein leading to the target segment(s). In this case a large posterolateral vein is seen to subtend the basal and mid inferior segments.

2.2.6 Target segment selection protocol

During the above steps, a guidance screen is displayed from which the clinician selects the target segments targeting areas of latest mechanical dyssynchrony (latest time to peak contraction i.e. minimum volume) in line with our previously published work.[155,175,222,223] All septal segments were excluded since epicardial LV stimulation in this region does not achieve effective cardiac resynchronisation. Segments with minimal volume change i.e. reduced endocardial strain were also excluded for selection given they likely represent regions of nonviability and is supported by previously published work linking LV placement in such regions with poor CRT outcomes.[125,155]

2.2.7 Intra-procedural CT Guided CRT workflow

1. Co-registration (image fusion) of the 3D LV endocardial mesh with fluoroscopic cine images was performed using three fluoroscopic projections: right anterior oblique (RAO) 30 degrees, posterior-anterior (PA) and left anterior oblique (LAO) 30 degrees. Bony landmarks, existing pacing wires +/- sternotomy wires were used to facilitate accurate image fusion as well as motion compensation. The co-registration algorithm has previously undergone validation using both cardiac models and patients undergoing CRT implantation.[218–220]

2. After CS cannulation was established, occlusive balloon venography was performed in three fluoroscopic projections (RAO 30 degrees, PA, LAO 30 degrees). These were then fused with the CT derived 3D shell (Figure 2-4A) and CS venogram (Figure 2-4B)

to confirm target vein locations as segmented by Cardiac CT and ensure a target vein ran through the target segment.

3. The RADI pressure wire protocol was performed as previously described.[175,224] The LV lead was temporarily placed in one or more non-target veins and the RADI pressure wire protocol was followed for each of these prior to attempting to deliver the LV lead

4. Finally, LV lead deployment was performed (in the usual fashion aiming to place the lead in the CT derived target segment (Figure 2-5) when coronary venous anatomy allowed and a target threshold of <2.5V @ 0.5 ms without phrenic nerve stimulation at 10V was achieved. A quadripolar LV lead was used in all cases ensuring the cathode was within the target segment where possible. Where a target vein did not exist in the target segment(s), the next adjacent and closest vein to the target segment was used. The RADI pressure wire protocol was also performed in the final LV lead position (for retrospective validation purposes) but did not dictate the final LV lead position.

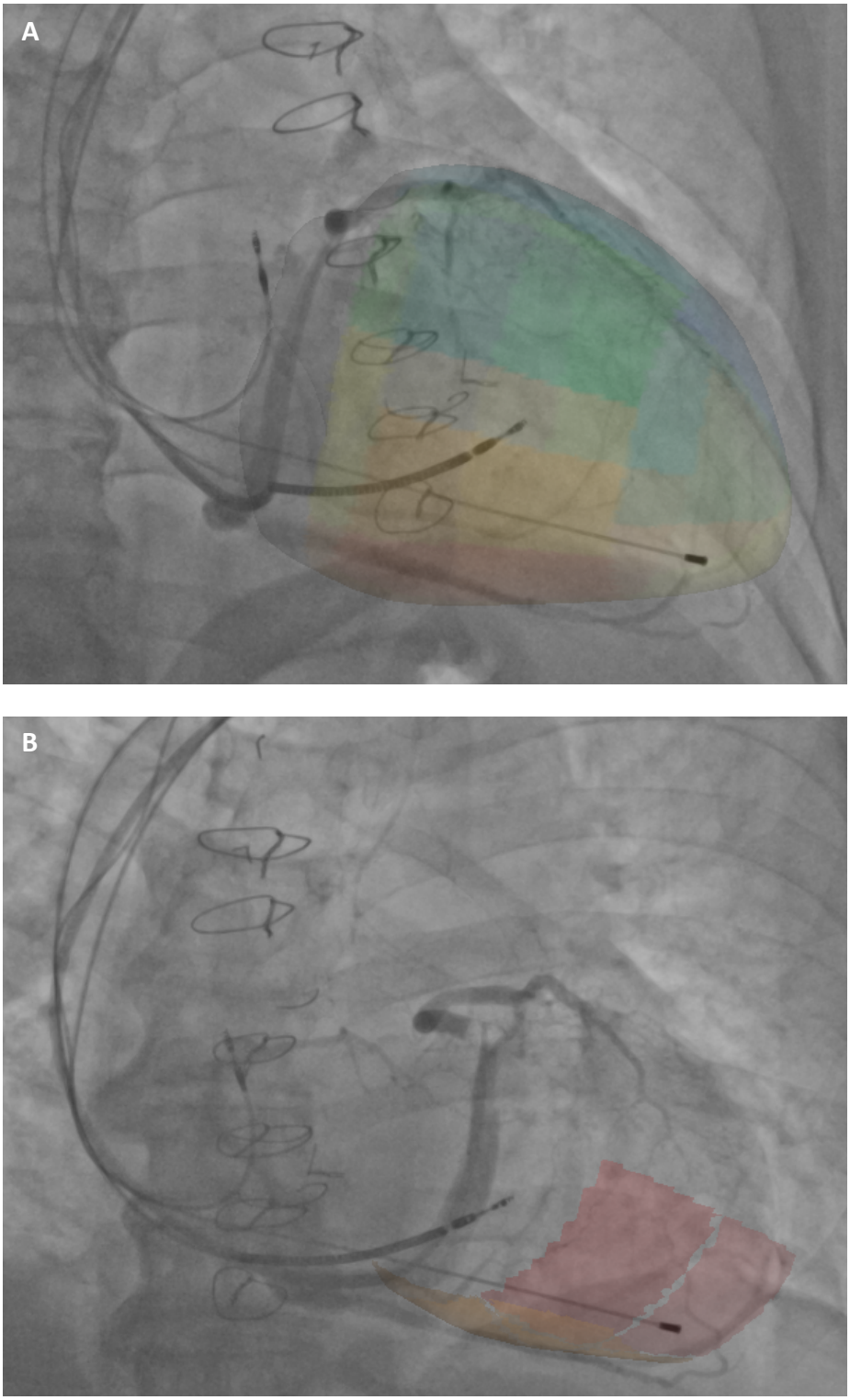


Figure 2-4: Occlusive balloon coronary venography

A) Fused with CT derived 3D mesh with 16 AHA segments

B) Fused with target AHA segment(s)

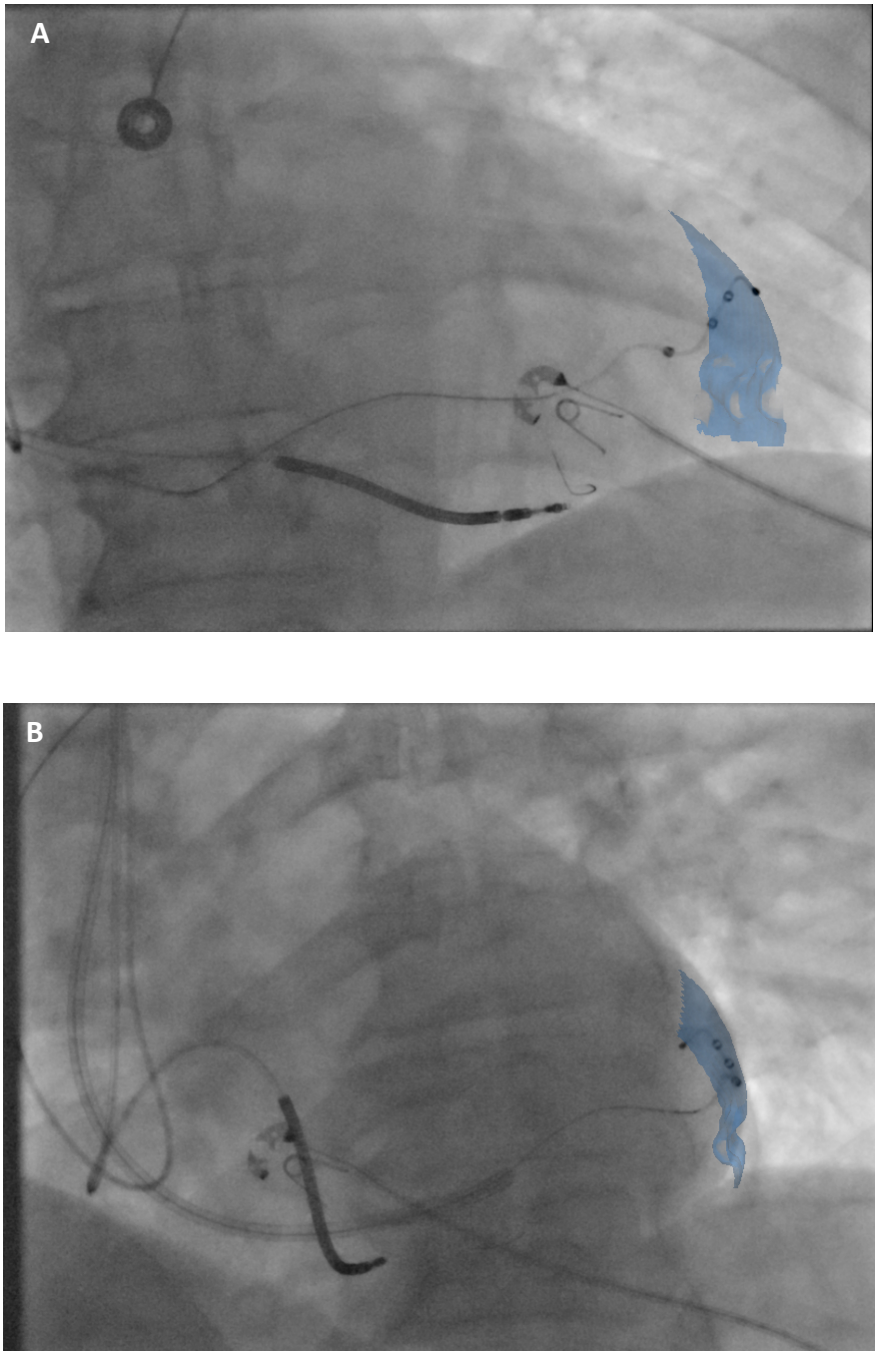


Figure 2-5: Real-time Cardiac CT image overlay guidance

Final LV lead position with the LV lead deployed in the mid-anterolateral AHA target segment 12 represented in:

A) Posterior-anterior projection

B) Left anterior oblique 30 degrees projection.

2.2.8 RADI pressure wire protocol

Invasive dP/dt_{max} measurements were performed using a 0.014-inch high-fidelity 'wireless' Pressure Wire X (St. Jude Medical, St. Paul, MN) in the LV cavity via a retrograde arterial approach as previously described.[175,224] Invasive dP/dt_{max} measurements were recorded using CoroFlow (Coroventis, Uppsala, Sweden) Patients with moderate to severe aortic valve stenosis, artificial aortic valves, aortopathy, aortic stent grafts or congenital aortic valve or sub-aortic valve pathology were not recruited to the study. Atrial pacing (AAI) 10 beats/min above the intrinsic rate or RV pacing (DDD) for patients with AF or no underlying rhythm was used for baseline dP/dt_{max} measurements. Atrioventricular delays were fixed at 100 ms and ventriculo-ventricular delay at 0 ms. The AHR for each venous site compared biventricular pacing with baseline (% change, dP/dt_{max}, mmHg/s). The AHR was retrospectively compared for those measured within CT target segments versus non-target segments. An AHR >10% was considered a positive result.

2.2.9 Statistical analysis

Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean$\pm$1SD or median [interquartile range]. Discrete variables were compared using Fisher's exact test. Normally distributed data were compared with a paired samples t-test. Non-normally distributed data were compared using Wilcoxon signed-rank testing. For all tests, $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences, Macintosh V 24.0.0.1 (2017). Armonk, NY, IBM Corporation.

2.3 Results

A total of 18 patients underwent the dedicated Cardiac CT research protocol for LV dyssynchrony and scar assessment. Baseline characteristics and pharmacological therapy are summarised in Table 2-1 and Table 2-2 respectively. Patients were predominantly male (n=17, 94.4%), had a moderately high percentage of RV pacing 60.0 ± 43.7% with a mean QRS duration of 154 ± 30 ms and just over half of the patients had ischemic cardiomyopathy (n=10, 55.6%).

Table 2-1: Baseline characteristics

Characteristic	Value
Age (years)	67.0 ± 9.9
Male gender	17 (94.4)
Ischaemic cardiomyopathy	10 (55.6)
NYHA III/IV	7 (38.9)
MLWHF questionnaire score	36.6 ± 23.5
6MWT distance (m)	316 ± 128
NT-proBNP (ng/mL)	1108.1 ± 767.3
Haemoglobin (g/L)	139.4 ± 13.8
Renal function (eGFR 60 mL/min/1.73m^2)	69.1 ± 21.0
QRS duration (ms)	154 ± 30
Left bundle branch block	15 (83.3)
CT Dose Length Product (mGycm)	1536 ± 701
Atrial fibrillation	9 (50)
Right ventricular pacing burden (%)	60.0 ± 43.7

Values are presented as mean ± SD or as n (%).

Table 2-2: Baseline pharmacological therapy

Pharmacological treatment	Value
ACE inhibitor/ARB/Sacubitril and Valsartan	18 (100)
Beta-blocker	16 (88.9)
Aldosterone antagonist	12 (66.7)
Loop diuretic	9 (50)
Anti-arrhythmic	4 (22.2)
Antiplatelet	7 (38.9)

Values are presented as n (%).

2.3.1 Cardiac CT planning outcomes

All 18 CT scans were completed successfully with a mean radiation dose length product (DLP) of 119.6 [IQR 106.9-204.9]cGycm^2 and mean supine CT scan time of 14.3 ± 2.0 minutes. CT post-processing (scar and dyssynchrony assessment to identify the optimal target segment) time was 23.9 ± 7.4 minutes giving a combined CT scan and processing time of 38.2 ± 6.0 minutes. Although we only observed late iodine enhancement in two patients in this study (Figure 2-6), we did identify clear regional hypoperfusion which was observed as hypoattenuation in keeping with scar tissue from previous myocardial infarction (Figure 2-7) in two further patients which correlated with regional LGE from historical CMR imaging where available. A further six patients had evidence of LV scar inferred by myocardial wall thinning and hypokinesis/akinesis but did not have visible late iodine enhancement or visible hypoperfusion. CT scar protocol B had superior reliability of visualising regional hypoattenuation compared to CT scar protocol A. Late

iodine enhancement was seen using both protocols but was not detected when expected to be visualised based on historical CMR imaging in some patients. Post-processing CT analysis identified the proposed target AHA segment subtended by a target coronary vein in all 18 patients.

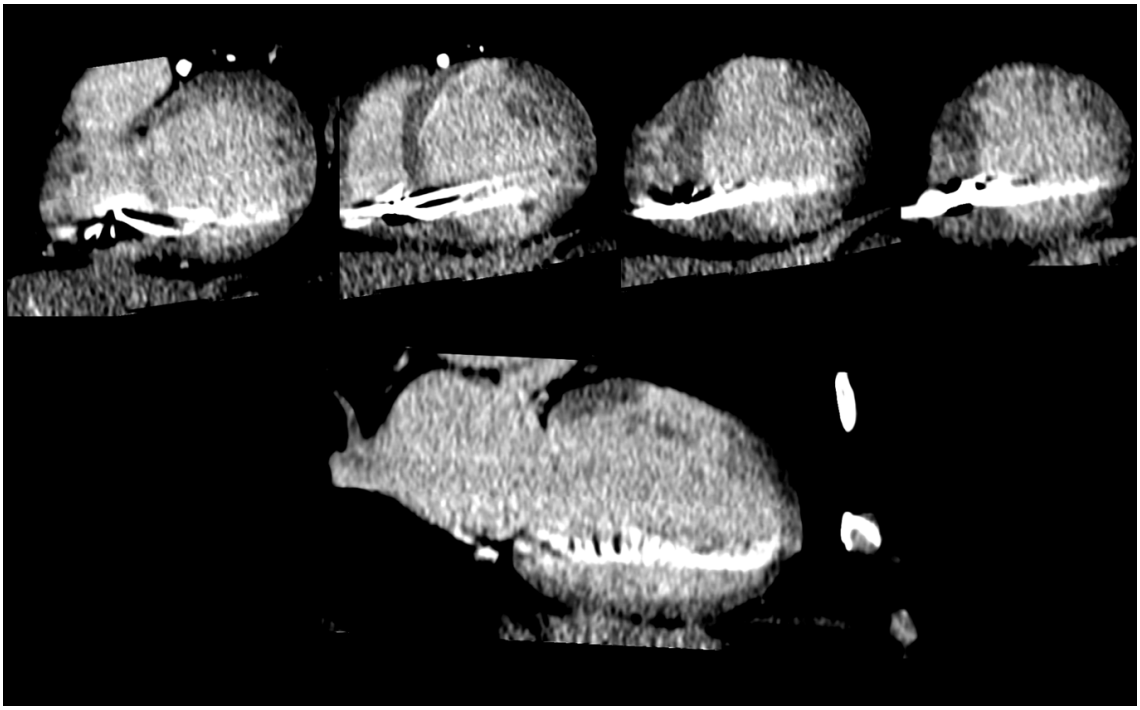


Figure 2-6: Late iodine enhancement seen with single energy cardiac CT (protocol B)

Images acquired with dynamic single energy cardiac computed tomography 12.5 minutes post contrast administration.

A) Series of short axis slices showing late iodine enhancement in the mid to apical anterior segments, extending into the mid anterolateral segment in keeping with prior left anterior descending (LAD) artery territory infarction.

B) Single 2 chamber slice showing transmural late iodine enhancement in the mid anterior segment.

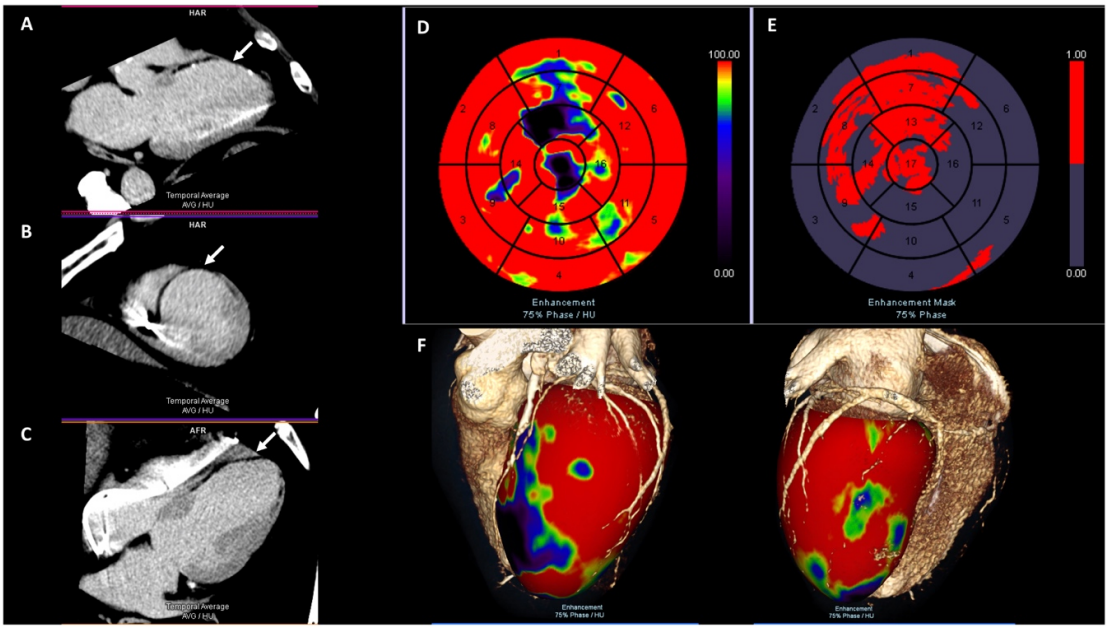


Figure 2-7: Cardiac CT scar analysis

Images acquired with dynamic single energy cardiac computed tomography 12.5 minutes post contrast administration.

A) 3-chamber acquisition showing hypoattenuation (white arrow) in the basal anteroseptal, mid anteroseptal and apical anterior segments

B) Short axis slice showing hypoattenuation (white arrow) in the mid anterior and anteroseptal segments.

C) 2-chamber acquisition slice showing hypoattenuation (white arrow) in the basal to apical anterior segments

D) AHA 17 segment polar plot of the left ventricle for first pass enhancement mapping (75% phase).

E) AHA 17 segment polar plot of the left ventricle for enhancement mask mapping (75% phase).

F) Hybrid view of volume rendered cardiac CT angiography images with colour coded first pass enhancement projected on the epicardial model of the left ventricle.

The fully retrospective scan showed a corresponding area of dyssynchrony and myocardial wall thinning. Hypoperfusion on the resting scan was observed and reduced wall motion compatible with scar tissue. Using dynamic perfusion at 12.5 minutes post 120mL iodinated contrast injection, although there was no delayed iodine enhancement, we did identify hypoperfusion which was observed as hypoattenuation (white arrows) over the infarcted LAD territory in keeping with scar tissue. This raises an interesting

question as to whether all scar actually hyper-enhances and in fact may be seen as hypoattenuating areas in patients with advanced scar formation.

To better assess the contrast in the myocardium CT data can be displayed with a colour coded overlay based on the HU values or an enhancement mask only colour coding the relatively low contrasted regions on top of the left ventricular myocardium, based on the first pass enhancement data.

2.3.2 CT guided CRT implant outcomes

A total of 17/18 (94%) patients underwent successful LV lead implantation with delivery to the CT derived target vein subtending the target AHA segment in 16/18 (89%) of patients (Table 2-3) and the LV lead was deployed in the CT derived target AHA segment in 15/18 (83%) of patients (Table 2-3). In the three patients where the LV lead was not deployed within the target AHA segment, one patient had phrenic nerve stimulation with all available vectors, one patient did not have a target vein of suitable calibre to pass a lead which had been anticipated on the pre-procedural CT scan and one patient had an unsuccessful LV lead implantation due to an acute angle from the right atrium (RA) into the coronary sinus (CS) preventing intubation with a catheter or guide sheath that was not apparent on the pre-procedural cardiac CT. Mean time from CS intubation to final LV lead deployment was 59 ± 26 minutes and complete implant procedural time (skin incision to closure) was 142 ± 47 minutes. Mean fluoroscopy run time was 28.2 ± 13.4 minutes with a median fluoroscopy radiation dose area product (DAP) of 1444 [IQR 947-2170] cGycm^2 and a mean implant contrast dose was 86.1 ± 49.4mL.

Table 2-3: Feasibility and safety of CT guided CRT

Variable	Value
Feasibility of CT guided LV lead placement in target vein	16/18 (89)
Feasibility of CT guided LV lead placement in target AHA segment	15/18 (83)
All-cause mortality	0
Heart failure hospitalisation	0
Other cardiovascular hospitalisation	2/18 (11)[a]
Intra-procedural related complications	1/18 (5.6)[b]

Values are presented as n (%). Feasibility of using real-time cardiac CT image overlay guidance, placing the LV lead in the CT-derived target vein and target segment and maintaining CRT pacing at 6 months.

[a] One patient was admitted for angina which was treated with optimisation of anti-anginal medication. The second represents the patient with unsuccessful LV lead implantation who went on to have a leadless LV endocardial pacing system (WiSE CRT, EBR systems, Sunnyvale, CA, USA).

[b] One patient became hypotensive with evidence of cardiac tamponade upon removal an externalized RV lead at the end of procedure and therefore was deemed not to be related to the image guidance element of the procedure. The patient was managed with a pericardial drain without the need to progress to emergency thoracotomy. The patient previously had a device implanted that became infected and had undergone transvenous lead extraction two weeks prior.

2.3.3 CT planning and CT guided outcomes

Total CT guided procedure time including CT scan, post-processing and implant time was 172.7 ± 59.6 minutes. Total CT and implant contrast dose were 201.3. ± 52.1mL. Echocardiographic and clinical measures at baseline and six-months follow-up are

shown in Table 2-4. LVESV was improved at six months compared to baseline (133.8 ± 67.7 vs. 103.5 ± 53.9mL, *p*=0.003). Furthermore, LVEDV, NYHA functional class and paced QRS duration were significantly lower at six months compared to baseline (Table 2-4). MLWHFQ scores, 6MWT distance and NT-proBNP were similar at six months follow-up compared to baseline (Table 2-4).

Table 2-4: CRT response - echocardiographic and clinical measures at baseline and six-month follow-up

Variable	Baseline	6-month follow-up	*p* value
LVEDV (mL)	200.8 ± 75.8	178.0 ± 63.2	0.028
LVESV (mL)	133.8 ± 67.7	103.5 ± 53.9	0.003
LVEF (%)	36.2 ± 9.4	44.2 ± 11.2	0.038
NYHA functional class	2.1 ± 0.6	1.5 ± 0.7	0.031
MLWHFQ score	30.9 ± 23.6	27.3 ± 24.2	0.266
6MWT distance (m)	341.8 ± 124.5	383.8 ± 138.1	0.178
NT-proBNP (pg/mL)	1161.6 ± 903.9	1163.4 ± 1435.9	0.997
Paced QRS duration (ms)	168.9 ± 29.8	134.2 ± 21.4	0.008
All comers QRS duration (ms)	154.6 ± 34.8	134.2 ± 21.4	0.082

All values are presented as mean ± SD. Absolute and percentage change values are the difference between values obtained from baseline pre-assessment visit and 6-month follow-up measures. Paced QRS duration excludes patients with recorded intrinsic QRS durations at baseline i.e. those that had a low RV pacing burden. All comers QRS duration reflects the change in QRS duration regardless whether paced or not at baseline and 6/12 follow-up.

2.3.4 Validation of CT target with the acute hemodynamic response

Of the 17 patients that underwent successful LV lead implantation, acute hemodynamic data was achievable in 14 patients. In the three patients that did not have acute

hemodynamic data collected, this was due to poor patient compliance during the initial part of the LV lead upgrade procedure in one patient and therefore a pressure wire was deemed inappropriate. In the other two patients, there was malfunction of the RADI analysing equipment at the start of the procedure and therefore neither patient received a RADI pressure wire study.

CT dyssynchrony analysis identifying the target coronary vein subtending the area of LMA outside of scarred regions was compared with all sites where the AHR was measured (2 ± 1 coronary veins per patient). An average AHR >10% was considered a positive result and was achieved in 9/11 (81.8%) patients with an LV lead delivered to the CT targets segments compared to 3/11 (27.3%) patients with LV leads placed in the non-target segments (p=0.030). In two patients that had dP/dt_{max} (mmHg/s) data recorded, only a single AHR was recorded within the target segment with no comparative AHR in a non-target segment due to unfavourable coronary anatomy and in one of these cases a limited dissection of the CS occurred and therefore these were not be included in this specific comparative AHR analysis.

2.4 Discussion

The current study demonstrates for the first time the safety and feasibility of real-time dedicated CT-defined scar and dyssynchrony to successfully guide LV lead implantation for CRT delivery. Furthermore, pacing within CT-defined segments showed more favourable acute haemodynamics confirming the validity of this approach. The results of the present study builds upon our previous pilot CT work,[175] where we validated the use of offline pre-procedure CT dyssynchrony analysis to identify LMA segments as potential target segments for LV lead placement. Our previous work found that cardiac CT derived target segments correlated well with invasive AHR data during biventricular pacing when compared offline.[175] In the present prospective study, we have demonstrated that using real-time CT image overlay guidance to target the latest mechanically activating segment outside of scar in patients undergoing an LV upgrade to CRT procedure is feasible. Furthermore, real-time CT image overlay guidance led to an improvement in outcomes at 6-months post LV lead upgrade to CRT. In addition, LV leads placed in the CT target segments were more likely to have an AHR >10% compared to those placed in non-target segments (p=0.030) which has previously been demonstrated to predict chronic reverse remodelling.[224]

2.4.1 Feasibility of using real-time CT image overlay guidance for left ventricular lead placement

CT image overlay guidance was performed with acceptable implant procedural times, contrast volumes and radiation doses. Mean time from CS intubation to final LV lead

deployment was 58 ± 26 minutes allowing for invasive acute hemodynamic data to be acquired whilst pacing in multiple coronary veins which would have artificially lengthened the implant procedure time as well as increased the risk of coronary vein complications including CS dissection and/or cardiac tamponade. The DAP for CT guided LV lead upgrade procedures were similar to historical *de novo* CRT implant controls from our centre 1757.9 ± 982.9 cGycm^2 vs. 1893 ± 1965 cGycm^2 (*p*=NS). The combined CT scan and CT data processing time to generate dyssynchrony curves was lengthy at 38.2 ± 6.0 minutes mainly due to large CT data sets, however, this is something that can be greatly improved upon in future software iterations with full-automation of the process. More research into reliable LV scar detection using cardiac CT is required and there is a great need for standardization of CT scar imaging protocols.

The majority of patients undergoing an LV lead upgrade procedure to CRT had a successfully guided LV lead placement into the CT derived target segment (83%) representing the area of latest mechanical activation outside of ischaemic scar. Echocardiographic and clinical outcome measures at 6 months were favourable using a real-time CT image overlay approach and in particular there was a significant improvement in mean LVESV, LVEDV and LVEF compared to baseline volumetric measurements. The overall volumetric CRT response rate using CT guidance was 70% which is high given over half of the patients had ischaemic cardiomyopathy who have been reported to have much lower non-guided CRT response rates around 50-60%[132,215,225–228] In addition, volumetric response rates are considered hard end-points for measuring CRT response outcomes and are usually lower than clinical composite score derived CRT response rates. We did not perform a statistical analysis on outcomes in patients receiving an LV lead delivered into the target segment versus non-target

segment due to small numbers of patients receiving an LV lead in the non-target segment (n=2). However, the results presented suggest that a CT-guided approach may improve CRT response outcomes in patients undergoing an LV lead upgrade to CRT and therefore an appropriately powered, larger randomised controlled study of real-time CT image overlay guidance versus standard (non-guided) CT guidance is warranted.

2.4.2 Safety of using a CT guided approach

The main risk of using a CT guided approach is from additional ionising radiation from the retrospective CT scan required for the dyssynchrony assessment. However, this may be partially offset by potentially quicker implant procedure times and lower fluoroscopy radiation doses in the future due to improved pre-procedural planning of the optimal target vein subtending the optimal target AHA segment as well as intra-procedural real-time image overlay guidance of the CS ostium location and coronary anatomy (Figure 2-4) and (Figure 2-8). The use of a RADI pressure wire in the LV cavity in this study was to further validate the CT target segments with the AHR. Invasive AHR measurements carry a small risk of arterial injury and stroke as well as increasing procedural complexity including the use of heparin whilst the pressure wire is *in vivo*. Future CT guided LV lead implants will not require an invasive pressure wire for validation as this has now been achieved in two separate cohort of patients; the present study (n=14) and Behar et al. (n=15)[175]

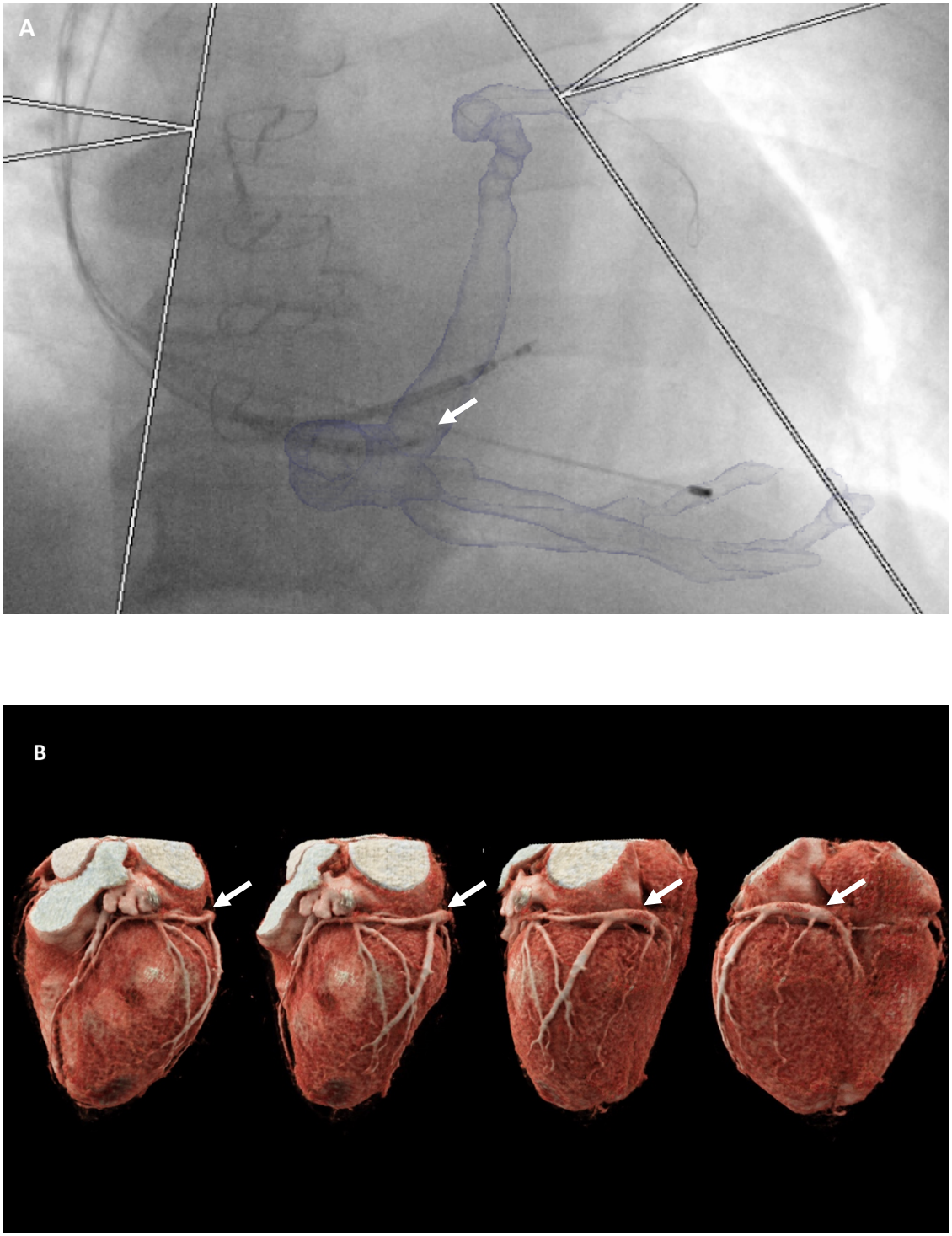


Figure 2-8: CT derived coronary venous anatomy

A) Overlaid onto fluoroscopy to aid operator with coronary sinus cannulation. CS guide (arrowed) is seen to enter the CS ostium and main CS body.

B) Volume rendered cardiac CT angiography images delineating the course of the coronary sinus (arrowed) and coronary venous anatomy.

2.4.3 Comparison with similar studies

Zhou et al. (2014) showed that reconstructing 3D LV venous anatomy from dual-view fluoroscopic venograms and fusing it with the LV epicardial surface on single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is feasible and technically accurate for guiding LV lead placement using a 17 segment AHA model.[229] Similarly, Sommer et al. (2013 and 2016) undertook a double-blind single centre randomised controlled trial to evaluate the clinical benefit of multimodality imaging-guided LV lead placement in CRT.[230,231] The study integrated CT derived CS anatomy, ^{99m}Technetium myocardial perfusion imaging and speckle-tracking echocardiography radial strain to target the optimal coronary vein closest to the non-scarred myocardial segment with latest mechanical activation in the image guided group (n=89). The control arm involved routine LV lead implantation in the posterolateral region with late electrical activation (n=93). In the image guided group significantly fewer patients met the primary endpoint of clinical non-response to CRT (26% vs. 42%, P= 0.02).[231] The study defined non-response to CRT as one or more of the following: (1) death, (2) heart failure hospitalisation or (3) no improvement in NYHA functional class and <10% increase in 6MWT distance.[231] Whilst the image guided group demonstrated greater improvement in absolute change in 6MWT at 6 months, there was no significant difference between groups for NYHA functional class or echocardiographic volumetric parameters.[231] This is in contrast to the findings in the present study and whilst there are no standardised ways to measure CRT response, we believe that volumetric response either on its own or as part of composite endpoint should be included when assessing techniques to improve CRT response outcomes.

Truong et al (2018) reported their findings using dual source cardiac CT to predict clinical outcomes in 54 patients scheduled for CRT in the DIRECT study.[154] This study did not use image guidance but interestingly 1:1 randomisation was performed and the implanting physician was given preimplant knowledge of coronary venous anatomy in half the patients. In the other half of patients, operators were blinded to the CT coronary venous anatomy and measurements were made of time to maximal wall thickness and inward wall motion to determine both CT global and segmental dyssynchrony as well as concordance of lead location to regional LV mechanical contraction.[154] The study identified that 72% of patients were clinical responders at 6-months follow-up using the heart failure clinical composite score and 17% had MACE at 2 years follow-up.[154] The study also found that both global wall motion and opposing anteroseptal-inferolateral wall motion individually predicted MACE. Furthermore, they identified that lead location concordant to regions of maximal wall thickness was associated with less MACE (p<0.01).[154] However, the DIRECT study failed to show that CT dyssynchrony metrics predicted 6-month CRT response and that myocardial scar (43%), posterolateral wall scar (28%), and total scar burden did not predict outcomes either. Furthermore, the study found that prior knowledge of coronary venous anatomy by CT did not reduce implant or fluoroscopy time.[154] These findings are in contrast to our previous retrospective CT work,[175] as well as the current study which uses real-time CT image overlay to guidance based on CT dyssynchrony indices and appears to have favourable volumetric outcomes when using real-time CT guidance.

More recently, Nguyên et al. (2019) successfully integrated a CS roadmap acquired from cardiac CT angiography, LGE imaging from Cardiac MRI and electrocardiographic imaging (ECGI) into a 3D CRT roadmap in 14 patients undergoing CRT implantation.[156]

Two further patients had CT and EGCI integration due to unusable MRI data in one patient and one patient did not undergo cardiac MRI due to a pre-existing device.[156] The LV lead was positioned outside scar in late-activated myocardium determined from ECGI in 11/14 patients that were implanted.[156] In the remaining three patients LV scar could not be avoided and in two patients cannulation of the initial target vein was not possible due to limited coronary venous anatomy.[156] The results of this feasibility study certainly show promise in targeting optimal LV lead placement, however, this is potentially a time and resource heavy pre-procedural planning exercise requiring two cardiac imaging modalities as well as ECGI analysis and integration. Nguyên et al. did not report the pre-procedural imaging and data processing/planning time which is likely to be reasonably long and may limit its clinical utility in real-world clinical practice. However, whilst LV scar imaging acquired from CMR is more reliable and reproducible than Cardiac CT at present,[180] if this were to change then CT and ECGI integration would certainly be a viable and potentially robust option for guiding LV lead implantation into the latest mechanically activating segment outside of scar.

Figure 2-9: Pre-procedural cardiac CT multi-planar reformat images of the coronary sinus indicating:

A) Presence of a Thebesian valve (arrowed)

B) Large left-sided superior vena cava (white arrow) draining into the coronary sinus (orange arrow) with complete absence of a right superior vena cava

2.4.4 Real-time Cardiac CT versus Cardiac MRI Guidance for CRT and Future Directions

We have previously demonstrated the feasibility of real-time CMR image guidance in a similar manner.[155] However, the advantage of cardiac CT over cardiac MRI in patients undergoing a device upgrade procedure is that there are no concerns around imaging CIEDs. Despite recent encouragement to image more patients with non-MRI conditional devices, this is not without risk in pacing dependent patients (44% were pacing dependent in the present study) and remains an absolute contraindication in patients with abandoned leads. Moreover, significant image degradation with pre-existing CIEDs limits the usefulness of CMR-based guidance platforms. There is also very little risk of claustrophobia with Cardiac CT and scans times are significantly quicker. Minimal breath holding is required with cardiac CT which is an important aspect to consider in the heart failure population who often struggle when supine for extended periods with repeated breath holds during multiple CMR acquisitions which may lead to image degradation. Cardiac CT also has the advantage over CMR as it can easily and rapidly image the coronary venous anatomy with submillimetre resolution which significantly helps with planning whether a target vein subtends the target AHA segment prior to the implant procedure. Additionally, preprocedural cardiac CT can identify potential complex anatomical challenges to aid with preprocedural planning and treatment decisions (Figure 2-9). Cardiac CT is also more widely available than CMR imaging in the majority of hospitals in the UK. However, LGE imaging with CMR remains superior to late iodine enhancement with cardiac CT, although there is a risk of nephrogenic systemic fibrosis with gadolinium contrast agents used in CMR, particularly in patients with renal impairment which is common in the heart failure population. In the present study,

cardiac CT did not reliably identify late iodine enhancement but instead, regional hypoperfusion, seen as hypoattenuating areas was observed and therefore more research into reliable LV scar detection using cardiac CT is required with standardization of CT scar imaging protocols. Additionally, use of cardiac CT may not be feasible in all patients because of significant renal impairment and given the small risks of ionising radiation this may not be an appropriate imaging modality for all groups of patients.

Integration of both modalities has recently been trialled by Nguyên et al.[156] however, using multiple imaging modalities adds significant cost and time which may limit its application to clinical care. Currently, we believe CMR guided LV lead implants are best suited to patients undergoing *de novo* image guided CRT implantation and CT guidance is more appropriate for patients with pre-existing devices undergoing LV lead upgrade to CRT. The TACTIC CRT study (A prospective randomised multi-centre **T**rial comparing c**A**rdiac MRI guided **C**RT versus conventional CR**T** implantation in patients with **I**schaemic **C**ardiomyopathy) is currently underway and is expected to complete recruitment of 218 patients by 2022 and will advise whether real-time CMR image overlay guidance is superior to standard care in patients with ischaemic cardiomyopathy undergoing *de novo* CRT implantation.

If late iodine enhancement protocols for cardiac CT improve and match the reliability of scar imaging obtained from CMR imaging, then cardiac CT may in the future become the imaging modality of choice for both *de novo* and upgrade image guided CRT procedures.

2.4.5 Study limitations

Our findings are subject to the inherent limitations of single centre, non-randomized controlled studies. However, this is a small proof of principle study and a larger multicentre, randomised controlled study would be necessary to evaluate whether real-time CT image overlay guidance is superior to standard care in patients undergoing an LV lead upgrade to CRT and is something we plan to undertake. Specifically, CRT response outcomes could not be compared for the 'out of CT target' group versus 'in CT target' group in the present study due to the small numbers of patients with LV leads delivered outside the target AHA segment (n=2) versus those delivered within the AHA target segment (n=8). Larger randomised controlled studies are therefore needed to investigate this further. In addition, although the co-registration algorithm has previously undergone validation using both cardiac models and patients undergoing CRT implantation,[218–220] there may still be a small margin of error unaccounted for in this study.

Left ventricular dyssynchrony was computed using motion tracking of the endocardial surface on retrospective cine imaging and volume over time curves were used to identify the latest mechanical activating segments as opposed to calculating pure strain with myocardial tagging. This could potentially neglect passive wall motion when only tracking the endocardial surface, however, similar tracking algorithms using both cardiac CT and CMR have shown good agreement with strain derived from myocardial tagging.[175,232,233] In addition, whilst the temporal resolution of cardiac CT in this study (up to 66ms) is greatly improved upon previous generations of CT scanners, this remains

inferior to echocardiography (20ms) and CMR (35-50ms obtained over multiple heart beats) and therefore cardiac CT may be less sensitive to subtle regional motion changes.

Given the expense of performing cardiac CT as well postprocessing of CT data to generate the target segments, this may not be feasible or cost-effective in some centres; however the data could be processed offsite and image-linked to the implanting site with the dyssynchrony assessment results and even target segment selection completed.

A large proportion of patients in this study had successful LV lead delivery to the CT derived target vein (89%) and AHA target segment (83%). Whilst we believe these numbers are acceptable for an image guidance approach, this remains a limitation of using a transvenous approach via the CS for LV lead delivery. Conversely, this may also be seen as an advantage of cardiac CT in preprocedural planning as we were able to reliably determine whether a target coronary vein subtended the target AHA segment. If preprocedural cardiac CT is able to reliably predetermine whether there is a suitable calibre vein subtending the target segment, then it could also be used to identify patients who are less likely to respond to conventional CRT and may be more suited to first-line endocardial LV lead implantation in order to reach the target segment. Left ventricular endocardial pacing may be useful in non-responders to conventional CRT.[234] However, the optimal site of stimulation varies greatly between patients.[235–237] The image guidance system may therefore help identify which patients are more suited to CT guided conventional CRT versus CT guided endocardial LV lead implantation which we have recently demonstrated using the WiSE CRT system (EBR systems, Sunnyvale, CA, USA).[238] We have also previously shown that such a targeted approach for

endocardial LV stimulation using CMR guidance to avoid scar results in improved hemodynamic response.[221,239]

2.5 Conclusion

Real-time cardiac CT image overlay guidance for optimal LV lead placement in delivering CRT is safe and feasible. There was significant improvement in echocardiographic volumetric response outcomes at 6-months follow-up compared to baseline and the overall CRT response rate was high given the large number of patients with ischaemic cardiomyopathy and use of volumetric response as a hard endpoint. Larger, multicentre, randomised controlled studies are needed to evaluate whether real-time CT image overlay guidance is superior to standard care in patients undergoing an LV lead upgrade to CRT.

Chapter 3: An interim analysis of Standard care versus TRIVEntricular pacing in Heart Failure (STRIVE HF): A prospective multicentre randomised control trial of triventricular pacing versus conventional biventricular pacing for cardiac resynchronisation therapy

3.1 Introduction

Cardiac resynchronisation therapy has be shown to improve symptoms and prognosis in selected patients with dyssynchronous heart failure. [4,31,32,240,241] However, a significant proportion of patients do not derive clinical benefit and/or show evidence of reverse remodelling assessed by 2D TTE.[103,241] There is a 30-50% non-response rate depending on heart failure aetiology and whether CRT response is assessed as an improvement in patient symptoms or the percentage of reverse remodelling using echocardiography volume and LVEF quantification. Poor patient selection, suboptimal LV lead positioning and insufficient delivery of cardiac resynchronisation are important causes of CRT non-response.[104–106]

One strategy to improve CRT response rates has focused on increasing the number of LV stimulation sites using multisite pacing which may improve CRT response by increasing the probability of pacing at an optimal site. In addition, by capturing more LV myocardium, a greater number of sites may provide faster and more physiological LV activation. Multisite LV pacing has the potential advantage over multipoint pacing using a quadripolar lead in that it allows a theoretical larger separation of the two LV electrodes. Multisite LV pacing with two LV leads may allow simultaneous recruitment of a larger volume of viable LV myocardium compared to single or multipoint LV pacing and therefore be more effective in reversing dyssynchrony.[187] Stimulating the LV using multisite LV pacing may capture the myocardium around areas of scar more effectively resulting in an improvement in CRT response. Previous studies have shown the

feasibility of multisite LV pacing and it has been shown to improve clinical parameters and ventricular reverse remodelling compared to biventricular pacing.[98,187–189]

Previous pathophysiological work has demonstrated a negligible benefit with increasing the number of LV pacing sites when an adequate response is achieved with BiV pacing, however this is also experimental data demonstrating that patients with scar and without functional block may benefit from novel pacing strategies such as multisite LV pacing.[187,190,191] Therefore patients with a high probability of a good response to BiV pacing (i.e. patients with a broad LBBB) are unlikely to obtain further benefit from implanting an additional LV pacing lead, however, there is a clinical need to try to improve response rates in patients with less clear indications for BiV pacing and multisite LV pacing offers a possible way for this to be achieved. The STRIVE HF (Standard care versus TRIVEntricular pacing in Heart Failure) trial was therefore designed to examine whether triventricular (TriV) pacing (two LV leads and one RV lead) in patients with LBBB with a moderately prolonged QRS duration of 120-150 ms was feasible and superior in terms of the proportion of patients who successfully reverse remodel (defined as a >15% reduction in LVESV on 2D TTE) compared to standard BiV pacing.

3.2 Methods

The STRIVE HF study currently has recruited 59 patients out of a target of 100 patients between 08 October 2015 and 04 October 2018 from 11 UK centres. All participants provided written informed consent. The study protocol was approved by the South East Coast Research Ethics Committee (Research Ethics Committee approval number 15/LO/0183) and conducted in accordance with the Declaration of Helsinki. This manuscript serves as an interim analysis of the STRIVE HF trial data.

3.2.1 Recruitment and follow-up

Consecutive patients undergoing CRT-D implantation for heart failure were screened for their eligibility. Patients who had class 1b indication for CRT (LBBB QRS 120-150ms) as per ESC guidelines 2013[137] were eligible for enrolment. Patients of any gender who were at least 18 years of age could participate in the study if they were able and willing to comply with all study requirements and able to give informed consent. Female participants of child bearing potential were allowed to participate in the study providing they ensured effective contraception was used during the study and for three months thereafter. Patients were not eligible if they had any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study. In addition, patients were not eligible if they had insufficient capacity to consent to the study, a QRS duration >150ms and non-LBBB morphology QRS duration 120-150ms. Female participants who were pregnant,

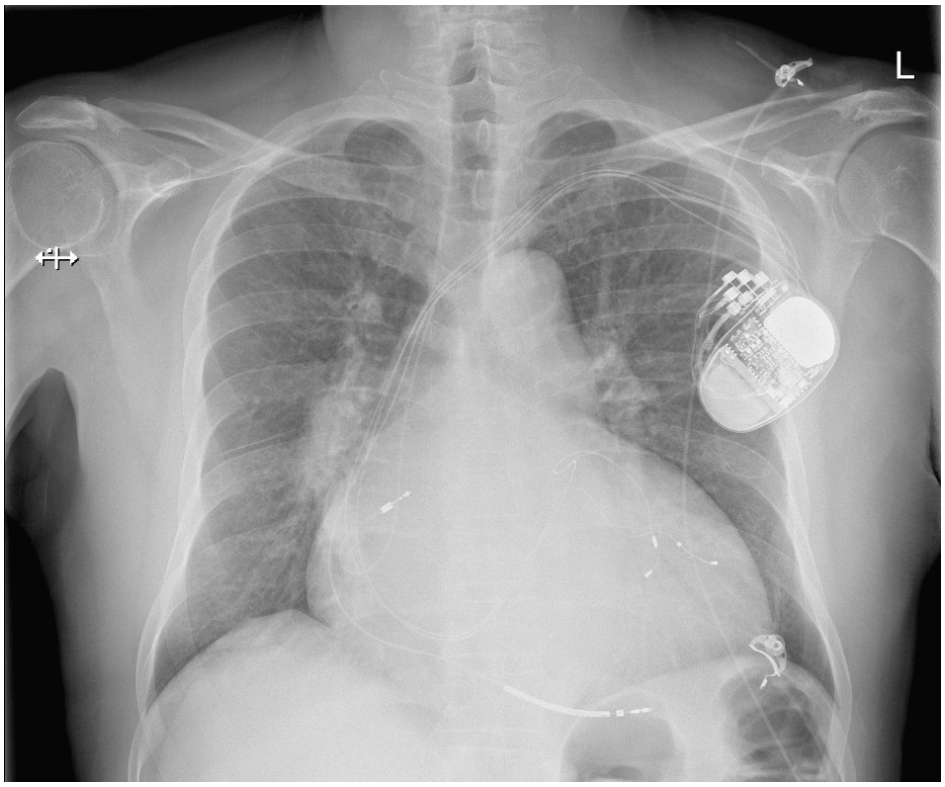
lactating or planning pregnancy during the course of the study were not eligible for enrolment.

All study participants were on optimal heart failure and/or antiarrhythmic therapy prior to device implantation. Eligible patients underwent the following tests at baseline and six-month follow-up visits: NYHA functional class assessment; physical examination; 12-lead resting ECG; 2D TTE (including Simpson's biplane assessment for LVEDV, LVESV and LVEF); MLWHFQ score (MLWHFQ); and 6MWT. In addition, patients underwent a full CRT device and pacing check at the six-month follow-up visit.

3.2.2 Randomisation

Enrolled patients were randomly assigned using the minimisation method in a 1:1 ratio to receive either a triventricular CRT-D (using one RV shock lead, two LV leads with maximal possible lead separation +/- RA lead as shown in Figure 3-1) or a conventional biventricular CRT-D (one RV shock lead, one LV lead and/or RA lead) and were stratified according to clinical centre, heart failure aetiology (ischaemic or non-ischaemic cardiomyopathy) and rhythm (sinus rhythm or atrial arrhythmia).

A



B

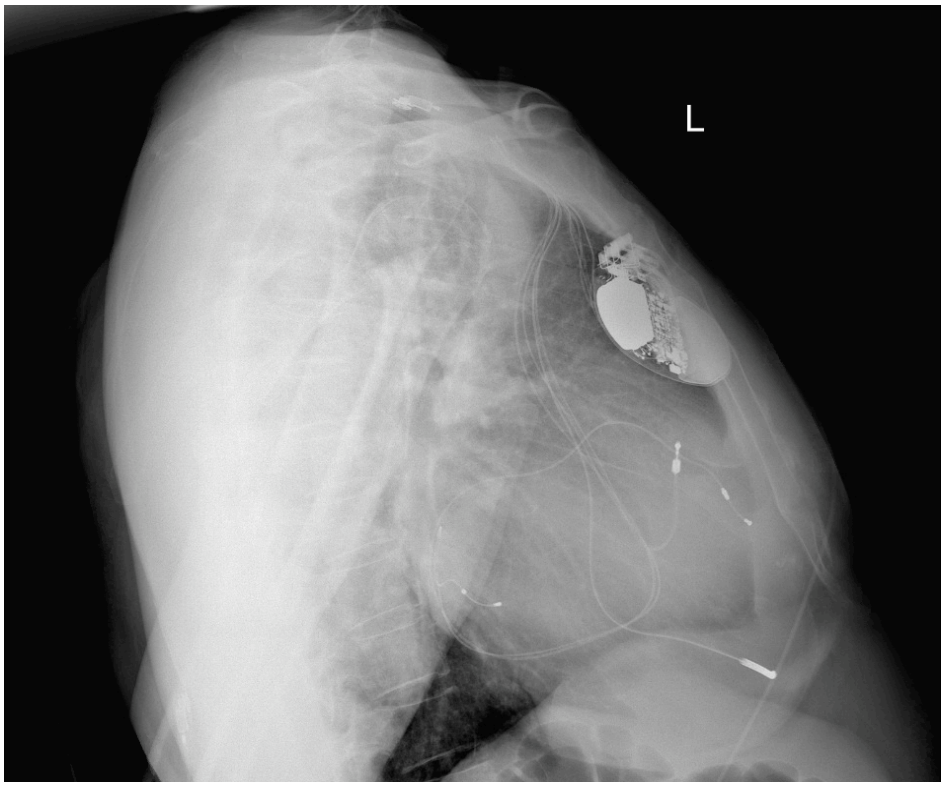


Figure 3-1: Representative posterior-anterior (A) and lateral (B) chest radiographs one day post implantation of a triventricular CRT defibrillator. Maximal left ventricular lead separation is best appreciated in the lateral chest radiograph.

3.2.3 Two-dimensional transthoracic echocardiographic studies

Left ventricular volumes (LVEDV and LVESV) were estimated by averaging those derived from the two-chamber and four-chamber windows according to Simpson's biplane method and the LV ejection fraction (LVEF) was calculated in the usual fashion. Transthoracic echocardiogram analysis was performed by experienced echocardiographers and consultant cardiologists competent at assessing LV volumes and LVEF using Simpsons biplane method who were both blinded to patient randomisation identifiers and study endpoints.

3.2.4 Implant procedure

An active fixation RV lead was positioned in the septum or RV apex according to operator preference and optimal lead parameters for both arms of the study. For patients randomised to triventricular device implantation, two LV leads were subsequently attempted to be implanted transvenously via the CS. Most operators performed two LV lead implantation using two of their preferred guide sheathes. Some operators elected to use the Worley^{TM} Advance Coronary Sinus Guide and LV lead delivery system (Merit Medical, South Jordan, UT, USA) and were able to successfully deliver two LV leads down a single guide sheath. Operators were instructed to aim for maximal LV lead separation as permitted by optimal lead parameters and absence of phrenic nerve stimulation e.g. The first LV lead (LV_1) was inserted, where possible, into a posterolateral or true lateral vein and the second LV lead (LV_2) as far as possible form LV1, in an anterior, high anterolateral or middle cardiac vein as governed by individual coronary venous anatomy. The two LV leads were connected to a triventricular capable device with an

integrated parallel Y port (Paradym TriV SonR CRT-D, ICV1231, MicroPort CRM, Clarmart, France, formerly Sorin and LivaNova CRM). A single LV output was programmed for all patients and acceptable thresholds were required for both LV pacing leads given individual LV outputs were not programable. Bipolar LV leads were used to connect to the IS-1 port on the triventricular device. For patients randomised to the biventricular control arm, quadripolar LV leads were used and connected to an IS-4 port. An active fixation right atrial (RA) lead was positioned in the RA appendage or RA free wall according to optimal lead parameters and absence of phrenic nerve stimulation for both arms of the study in patients deemed appropriate for RA lead implantation (i.e. those in sinus rhythm or expected to have a reasonable chance of maintaining sinus rhythm). The SonR (MicroPort CRM, Clarmart, France) auto-optimising RA lead was permitted to be used in both arms of the study. Once all the leads were sutured in place, electrical latency (Q-LV) was measured individually for each LV lead implanted during RV sensing and RV pacing but the results did not guide the final LV lead position.

Following CRT implantation, all devices were programmed with an AV delay of 100ms and simultaneous RV-LV pacing. Patients implanted with a SonR leads were allowed to have automatic AV optimisation switched on. All CRT implants had a company representative present for advice regarding lead and device implantation, equipment or device interrogation, however, they did not take part in the study design, data collection, analysis, interpretation of results, manuscript writing or in the decision to submit the paper for publication.

3.2.5 Definitions

Ischaemic cardiomyopathy was defined by standard criteria (prior myocardial infarction, presence of any epicardial coronary artery stenosis >75% or coronary revascularization with a scar pattern consistent with myocardial infarction on CMR imaging). Absence of the above criteria were defined as non-ischaemic cardiomyopathy (NICM). Triventricular pacing was defined as CRT with one RV lead and two LV leads and/or an RA lead. Biventricular pacing refers to CRT with one RV lead, one lead and/or an RA lead. LV pacing thresholds were defined as the first loss of capture on the LV channel.

3.2.6 Endpoints

The primary endpoint was feasibility of achieving and maintaining triventricular pacing at 6 months**,** calculated as the percentage of surviving patients still triventricular pacing at 6 months based on their pacing check. The exact percentage of triventricular pacing recorded by the device was not deemed to be important for assessing the feasibility of triventricular pacing as any reduction in RV-LV pacing would likely have occurred if the patient was implanted with either one or two left ventricular leads.

Secondary endpoints were as follows:

1. Proportionate effect of TriV vs. BiV pacing on reverse remodelling (comparison of % reduction in LVEDV)
2. Proportion of patients who successfully reverse remodel (defined as a reduction in end systolic volume >15% derived from 2D echocardiogram)

3. Proportionate effect of TriV vs. BiV pacing on reverse remodelling (comparison of % reduction in LVESV) in patients with prespecified subgroups of AF and heart failure aetiology
4. Proportion of patients who successfully reverse remodel (defined as a reduction in end systolic volume >15% derived from 2D echocardiogram) in patients with prespecified subgroups of AF and heart failure aetiology
5. Mean change in NTpro-BNP in patients with triventricular devices compared with biventricular devices (pg/mL)
6. Percentage change in NTpro-BNP in patients with triventricular devices compared with biventricular devices
7. Comparison of effect of biventricular and triventricular pacing on scores in MLWHFQ scores
8. Comparison of effect of biventricular and triventricular pacing on change in 6-minute walk test (metres)
9. Comparison of percentage of shocks delivered in triventricular arm vs biventricular arm.

Time to first heart failure hospitalisation, rate of adverse events and mortality rates during the study period were also recorded for both groups. All adverse events were reported to and adjudicated by the chief investigator and sponsor of the study (Guy's and St Thomas' NHS Foundation Trust) who reviewed the event type, severity and relatedness to an additional LV lead implant.

3.2.7 Statistical analysis

Data analysis was performed according to the intention-to-treat principle; patients who crossed over were analysed in their original treatment assignment. Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean±1SD. Discrete variables were compared using Fisher's exact test. Continuous data were assessed for normality with the Shapiro-Wilk test where $p \geq 0.05$ was considered normally distributed data. Normally distributed data were compared with an independent samples t-test. Non-normally distributed data were compared using the Wilcoxon signed-rank test. All statistical tests were 2-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences, Macintosh V24.0.0.1(2017). Armonk, NY:IBM Corporation.

3.3 Results

A total of 59 patients were randomised (TriV group n=30; control BiV group n=29) during the interim analysis study period. In the TriV group, a total of 27/30 patients were successfully implanted with a TriV system; a second LV lead was not able to be implanted in three patients who therefore received a BiV system but remained in their TriV group for the intention-to-treat analysis. In the BiV group, all 29 patients were successfully implanted with a BiV system. There were no deaths and no patients lost to follow-up in either group for the interim analysis period.

Baseline characteristics (Table 3-1) and pharmacological therapy (Table 3-2) were balanced between both groups.

Table 3-1: Baseline characteristics

Characteristic	BiV Group (n=29)	TriV Group (n=30)	All patients (n=59)	*p* value
Age (years)	68.0 ± 11.1	66.5 ± 10.2	67.2 ± 10.6	0.623
Male gender	21 (72.4)	23 (76.7)	44 (74.6)	0.771
Coronary artery disease	9 (31.0)	11 (36.7)	20 (33.9)	0.785
Ischaemic cardiomyopathy	19 (65.5)	20 (66.7)	39 (66.1)	1.000
Previous CABG	4 (13.8)	3 (10.0)	7 (11.9)	0.706
Previous valve surgery	4(13.8)	1 (3.3)	5 (8.5)	0.195
Hypercholesterolaemia	6 (20.7)	4 (13.3)	10 (16.9)	0.506
Current tobacco smoking	1 (3.4)	5 (16.7)	6 (10.2)	0.195
Previous history of tobacco smoking	7 (24.1)	4 (13.3)	11 (18.6)	0.333
Diabetes mellitus	14 (48.3)	12 (40.0)	26 (44.1)	0.604
Hypertension	11 (37.9)	11 (36.7)	22 (37.3)	1.000
Atrial fibrillation	8 (27.6)	5 (16.7)	13 (22.0)	0.360
Atrial flutter	2 (6.9)	1 (3.3)	3 (5.1)	0.612
QRS duration (ms)	138.2 ± 7.9	136.2 ± 9.0	137.2 ± 8.5	0.418
LVEF (%)	29.5 ± 5.4	25.9 ± 7.3	27.7 ± 6.6	0.115
LVEDV (mL)	174.5 ± 43.1	180.8 ± 82.6	177.7 ± 65.7	0.515
LVESV (mL)	125.6 ± 38.9	136.3 ± 70.9	131.1 ± 57.2	0.883
Impaired RV systolic function	8 (29.6)	8 (28.6)	16 (29.1)	1.000
Systolic blood pressure	123.8 ± 16.0	120.1 ± 12.5	121.8 ± 14.1	0.360
6MWT distance (m)	295.0 ± 140.7	313.6 ± 175.5	305.2 ± 159.5	0.520
MLWHFQ score	34.8 ± 22.6	44.9 ± 22.9	40.0 ± 23.1	0.110
NT-proBNP (pg/mL)	1865.8 ± 2128.0	1439.7 ± 1676.3	1648.0 ± 1900.7	0.723
NYHA functional class III/IV	7 (24.1)	10 (33.3)	17 (28.8)	0.567

Values are presented as mean ± SD or as n (%).

Table 3-2: Baseline pharmacological therapy

Pharmacological treatment	BiV Group (n=29)	TriV Group (n=30)	All patients (n=59)	*p* value
ACE inhibitor or ARB	27 (93.1)	27 (90)	54 (91.5)	1.000
Beta-blocker	25 (86.2)	28 (93.3)	53 (89.8)	0.424
Aldosterone antagonist	18 (62.1)	25 (83.3)	43 (72.9)	0.084
Loop diuretic	19 (65.5)	19 (63.3)	38 (64.4)	1.000
Aspirin	15 (51.7)	15 (50.0)	30 (50.8)	1.000
Clopidogrel	2 (6.9)	4 (13.8)	6 (10.3)	0.670
Oral anticoagulant	14 (48.3)	10 (34.5)	24 (41.4)	0.424
Statin	18 (62.1)	16 (55.2)	34 (58.6)	0.790

Values are presented as n (%).

In the BiV group, the LV lead was positioned in the anterior vein in 2 patients (%), an anterolateral vein in 3 patients (%), a lateral vein for 11 patients (%), a posterolateral vein in 10 patients (%), a middle cardiac vein in 1 patient (%) and 2 final LV locations were unknown. In the TriV group, the LV leads were positioned in the anterior and anterolateral veins in 1 patient (3%), the anterior and lateral veins in 3 patients (10%), the anterior and posterolateral veins in 4 patients (13%), the anterior and middle cardiac veins in 1 patient (3%), the anterolateral and posterolateral veins in 7 patients (23%), the anterolateral and lateral veins in 4 patients (13%), the lateral and middle cardiac veins in 2 patients (7%) and in the lateral and posterolateral veins in 5 patients (17%). In the 3 patients that had an unsuccessful 2nd LV lead implants, a single LV lead was implanted in the posterolateral vein in 2 patients (7%) and in the anterolateral vein in 1 patient (3%).

Mean procedure duration was significantly higher in the TriV group (183.9 ± 77.1 vs. 132.7 ± 49.0 minutes, *p*=0.007) as was the mean duration from CS intubation to final LV lead placement (76.8 ± 40.5 vs. 45.4 ± 31.6, *p*=0.001). Mean fluoroscopy times were significantly longer in the TriV compared to BiV group (41.4 ± 19.9 vs. 28.5 ± 17.8 minutes, *p*=0.005). Radiation doses were non-significantly higher in the TriV group (3335 ± 2930 vs. 2361 ± 1990 cGycm^2, *p*=0.386). Mean contrast volume was non-significantly higher in the TriV vs. BiV groups (80.7 ± 56.3 vs 63.40 ± 37.9 mL, *p*=0.372). Mean LV pacing thresholds at implant were significantly higher in the TriV group (1.65 ± 0.70 vs. 1.01 ± 0.54 V, *p*=0.001), with similar LV lead pulse widths (0.57 ± 0.25 vs. 0.45 ± 0.13 ms, *p*=0.135) and similar LV lead impendences between TriV and BiV groups (757.4 ± 304.7 vs. 846.6 ± 293.8 Ω, *p*=0.222). There were no significant differences in all-cause mortality, heart failure hospitalisation, other cardiovascular hospitalisation or a composite of all three of these endpoints (Table 3-3).

Table 3-3: Feasibility and safety of biventricular versus triventricular pacing

Variable	BiV Group (n=29)	TriV Group (n=30)	All patients (n=59)	*p* value
Feasibility of CRT	29 (100)	23/28 (82.1%)[a]	52/57 (91.2%)	0.023
All-cause mortality	0	0	0	
HF hospitalisation	1 (3.4)	0	1 (1.7)	0.492
Other CV hospitalisation	1 (3.4)	4 (13.3)	5 (8.5)	0.353
Composite of all-cause mortality, HF and other CV hospitalisation	2 (6.9)	4 (13.3)	6 (10.2)	0.671
Percentage of appropriate ICD shock therapy (%)	1 (3.4)	1 (3.3)	2 (3.4)	1.000

Values are presented as n (%). Feasibility of achieving and maintaining triventricular pacing at 6 months is calculated as the percentage of surviving patients still triventricular pacing at 6 months based on their 6-month pacing check.

[a]Two patients in the TriV group did not have sufficient data documented to determine whether they were TriV pacing or not and were therefore excluded from this calculation.

3.3.1 Primary endpoint

Feasibility of achieving and maintaining CRT at 6 months was significantly lower in the TriV versus BiV group (82.1%, n=23 vs 100%, n=29, *p*=0.023) (Table 3-3).

Table 3-4: Echocardiographic and clinical measures at baseline and six-month follow-up

Variable	BiV Group (n=29)	TriV Group (n=30)	*p* value
LVEDV (mL)			
Baseline	174.5 ± 43.0	180.8 ± 82.6	
Follow-up	156.0 ± 59.3	175.3 ± 84.8	
Absolute change (mL)	-18.6 ± 56.1	-5.5 ± 51.2	0.101
Percentage change (%)	-8.6 ± 31.2	-2.3 ± 22.4	0.377
LVESV (mL)			
Baseline	125.6 ± 38.9	136.3 ± 70.9	
Follow-up	106.4 ± 51.4	121.1 ± 73.7	
Absolute change (mL)	-19.3 ± 55.3	-15.2 ± 40.8	0.500
Percentage change (%)	-11.2 ± 40.3	-11.6 ± 25.9	0.959
LVEF (%)			
Baseline	29.5 ± 5.4	25.9 ± 7.3	
Follow-up	35.6 ± 9.3	33.0 ± 9.0	
Absolute change (%)	6.1 ± 9.9	8.0 ± 10.8	0.499
NT-proBNP (pg/mL)			
Baseline	1865.8 ± 2128.0	1439.7 ± 1676.3	
Follow-up	1937.0 ± 2559.8	1801.4 ± 2608.7	
Absolute change (pg/mL)	296.5 ± 2085.2	600.5 ± 2464.2	0.354
Percentage change (%)	131.2 ± 546.2	70.1 ± 152.5	0.248
MLWHFQ score			
Baseline	34.8 ± 22.6	44.9 ± 22.9	
Follow-up	28.5 ± 21.4	32.5 ± 23.5	
Absolute change	-4.2 ± 21.1	-13.7 ± 24.7	0.136
Percentage change (%)	57.8 ± 221.7	-16.9 ± 70.9	0.180
6MWT distance (m)			
Baseline	295.0 ± 140.7	313.6 ± 175.5	
Follow-up	271.0 ± 146.7	319.2 ± 170.5	
Absolute change (m)	**-35.8 ± 84.6**	**23.0 ± 72.9**	**0.016**
Percentage change (%)	-6.6 ± 34.0	31.1 ± 95.2	0.133
NYHA functional class			
Baseline	2.3 ± 0.5	2.3 ± 0.5	
Follow-up	1.9 ± 0.7	2.0 ± 0.8	
Absolute change	-0.4 ± 0.8	-0.3 ± 0.7	0.839
Percentage change (%)	-18.4 ± 34.9	-14.4 ± 31.2	0.714

All values are presented as mean ± SD. Absolute and percentage change values are the difference between values obtained from baseline pre-assessment and 6-month follow-up measures.

3.3.2 Secondary endpoints

1. There was no significant difference in absolute change or percentage change of LVESV (mL) from baseline to 6-month follow-up between TriV and BiV groups (Table 3-4).
2. There was no significant difference in the number of patients that reverse remodelled (i.e. the number of volumetric responders defined by a reduction in LVESV >15% on TTE) between TriV and BiV groups (40% vs. 51.7%, *p*=0.438) (Table 3-5).
3. There was no significant difference in absolute change or percentage change of LVESV (mL) from baseline to 6-month follow-up between TriV and BiV groups in patients with sinus rhythm, AF, ICM or NICM (Table 3-6).
4. There was no significant difference in the number of patients that reverse remodelled between TriV and BiV groups in patients with sinus rhythm, AF, ICM or NICM (Table 3-5).
5. There was no significant difference in absolute change of NTpro-BNP (pg/mL) from baseline to 6-month follow-up between TriV and BiV groups (Table 3-4).
6. There was no significant difference in percentage change of NTpro-BNP from baseline to 6-month follow-up between TriV and BiV groups (Table 3-4).
7. There was no significant difference in absolute change or percentage change of MLWHFQ scores from baseline to 6-month follow-up between TriV and BiV groups (Table 3-4).
8. There was no significant difference in percentage change of 6MWT distance (m) from baseline to 6-month follow-up between TriV and BiV groups, although absolute change in 6MWT distance was significantly higher in the BiV group (Table 3-4).

9. The mean number of recorded ICD shocks was similar between TriV versus BiV groups (3.4%, n=1 vs. 3.3%, n=1, *p*=1.000) (Table 3-3).

In addition, there was no significant difference in absolute change or percentage change of LVEDV and LVEF values from baseline to 6-month follow-up between TriV and BiV groups (Table 3-4). Battery longevity (defined as the elective replacement index on the device) was significantly lower in the TriV group (6.0 ± 2.4 vs. 8.6 ± 3.1 years, *p*=0.005).

Table 3-5: Reverse remodelling outcome measures in the entire cohort and subgroups of atrial fibrillation and heart failure aetiology

Number of volumetric responders for the entire cohort and prespecified subgroups:	**BiV Group (n=29)**	**TriV Group (n=30)**	**All patients (n=59)**	***p* value**
Entire cohort	15 (51.7)	12 (40.0)	27 (45.8)	0.438
Atrial fibrillation	5 (62.5)	3 (60.0)	8 (61.5)	1.000
Sinus rhythm	9 (47.4)	9 (37.5)	18 (41.9)	0.550
Ischaemic cardiomyopathy	8 (42.1)	5 (25.0)	13 (33.3)	0.320
Non-ischaemic cardiomyopathy	7 (70.0)	7 (70.0)	14 (70)	1.000

Values are presented as n (%). Volumetric response was defined as LVESV >15% reduction on two-dimensional transthoracic echocardiography.

Table 3-6: Left ventricular end-systolic volumes at baseline and six-month follow-up for heart rhythm and heart failure aetiology subgroups

Variable	BiV Group (n=29)	TriV Group (n=30)	*p* value
LVESV (mL) for SR subgroup			
Baseline	130.1 ± 44.1	131.3 ± 70.2	
Follow-up	112.6 ± 54.6	122.9 ± 79.5	
Absolute change (mL)	-17.5 ± 61.2	-8.4 ± 30.3	0.529
Percentage change (%)	-7.4 ± 42.6	-8.8 ± 26.3	0.900
LVESV (mL) for AF subgroup			
Baseline	124.0 ± 24.5	162.3 ± 84.3	
Follow-up	92.9 ± 45.3	114 ± 54.3	
Absolute change (mL)	-31.1 ± 43.2	-48.3 ± 71.6	0.596
Percentage change (%)	-25.0 ± 33.2	-25.9 ± 24.0	0.959
LVESV (mL) for ICM subgroup			
Baseline	122.1 ± 32.3	135.6 ± 74.7	
Follow-up	113.3 ± 56.1	134.2 ± 82.3	
Absolute change (mL)	-8.7 ± 59.6	-1.4 ± 24.5	0.613
Percentage change (%)	-3.8 ± 44.4	-3.2 ± 23.1	0.956
LVESV (mL) for NICM subgroup			
Baseline	132.4 ± 50.5	137.8 ± 66.5	
Follow-up	93.1 ± 40.3	94.9 ± 45.3	
Absolute change (mL)	-39.3 ± 41.6	-42.9 ± 53.1	0.956
Percentage change (%)	-25.2 ± 27.7	-28.5 ± 23.6	0.774

Values are presented as mean ± SD. Absolute and percentage change values are the difference between values obtained from baseline and 6-month follow-up measures.

3.4 Discussion

The STRIVE HF study was a randomised multicentre study designed to evaluate the feasibility, safety and clinical value in improving CRT response of TriV compared to standard BiV pacing in patients undergoing CRT-D implantation who had class 1b indications for CRT (LBBB QRS 120-150ms) as per ESC guidelines 2013.[137]

Implanting two LV leads and maintaining triventricular pacing at 6 months was feasible in 82.1% of patients which we considered satisfactory, however, this was significantly lower compared to the feasibility of maintaining BiV pacing in 100% of the control group. Two LV leads were successfully implanted in 27/30 (90%) patients randomised to the TriV group. In three patients in the TriV group where addition of a second LV lead was not technically possible, these patients received a biventricular pacing system with a single LV lead instead; in one patient, this was due to a combination of poor pacing parameters with high LV thresholds and presence of phrenic nerve stimulation in the remaining available coronary veins for a second LV lead; in the other two patients, the attempt at adding a second LV lead was abandoned due to difficult CS cannulation in both patients, with a limited CS dissection occurring in one of these patients with no evidence of cardiac tamponade or any long-term sequalae. Whilst there were no reported lead displacements in the 6-month follow-up period in either, there were several reports from multiple sites of technical difficulties with lead stabilities, suboptimal pacing parameters and difficulties in avoiding phrenic nerve stimulation. Furthermore, there was an additional report of CS dissection in one patient who did receive and maintain TriV pacing at 6-months. The study protocol required maximal LV

lead separation. Not infrequently, placing a single LV lead in the coronary venous system can be technically challenging, often governed by either complicated coronary venous anatomy, poor lead stability, suboptimal LV pacing thresholds or presence of phrenic nerve stimulation. Unsurprisingly, this was even more challenging when attempting to place two LV leads in the coronary venous circulation with even more limitations, therefore resulting in the second LV lead being implanted where was feasible rather than where was desirable.

3.4.1 Safety of triventricular pacing

The short-term safety profile of triventricular pacing was satisfactory with no recorded deaths or procedure related major complications for the interim study period. There were no reports of device related infection during the 6-month study period in either of the two groups. The use of an internal Y-connector as opposed to an external Y-connector made implantation of the TriV system more straightforward for operators. However, assessing both LV lead thresholds was not always straightforward at the pacing check follow ups and in some cases difficult to ascertain whether the two LV lead thresholds were identical or whether there was no capture from one of the LV leads to explain why we only saw one change in morphology during LV lead testing. Threshold rises were observed in 16/30 patients in the TriV group at the 6-month follow-up and in 5 of these patients, TriV pacing was deactivated by lowering the LV lead output to a threshold below the highest LV whilst still remaining high enough for the other LV lead in an attempt to preserve battery longevity and provide the patient with BiV instead of TriV pacing for their ongoing clinical care outside of the study. A few cases of phrenic nerve stimulation were reported following implant during the study period which were

resolved by reprogramming the LV output channel. Furthermore, TriV pacing with two LV leads was associated with significantly shorter battery longevity compared to biventricular pacing with a single LV lead.

All primary and secondary and secondary endpoints were negative in the STRIVE HF interim analysis, apart from absolute change in 6MWT distance which was significantly higher in the BiV group (Table 3-4). However, we do not feel this statistically significant finding is clinically relevant, not least due the fact that patients in the BiV group walked on average 35.8 metres less at 6-month follow-up compared to their baseline scores and patients in the TriV group walked 23.0 metres more compared to their baseline scores. This statistical finding is not supported by the percentage change in 6MWT scores (Table 3-4) at baseline compared to 6-months which was not significantly different between TriV and BiV groups. Importantly, there was no evidence of superior remodelling benefit in the TriV group compared to BiV group and in fact the CRT response rate using LVESV>15% to define CRT response, was lower in the TriV group (40%) versus the BiV group (51.7%). Taking this together with the fact that mean battery longevity was significantly shorter (due to higher mean LV pacing thresholds) with longer procedure durations (driven by longer time spent deploying LV leads in the coronary venous system) and longer mean fluoroscopy times in the TriV group, we did not find any evidence to support the use of Triventricular pacing in patients with a class 1B indication for CRT (LBBB QRS 120-150ms) as per the ESC guidelines 2013.[137] This remained the case in pre-specified subgroups of patients with sinus rhythm, AF and ischaemic and non-ischaemic heart failure aetiology. However, this is an interim analysis of the study results and therefore the results are not sufficiently powered to make any firm conclusions at this stage and therefore we eagerly await the final STRIVE HF analysis once recruitment

is completed. We did not find any major concerns in terms of safety endpoints and therefore believe the STRIVE HF study continue to recruit to the target number of patients (n=100).

3.4.2 Comparison with similar studies

Initial studies of multisite pacing were for the most part undertaken in single centres and offered positive results compared to the present trial. Rogers et al demonstrated a significant improvement in 6MWT distance, MLWHFQ scores, peak VO2, and LV ejection fraction at 6 months when comparing conventional *de novo* biventricular stimulation with *de novo* triventricular stimulation.[98] This study had two TriV groups: group A had two LV and one RV lead implanted and Group B had two RV and one LV leads implanted. Notably, the improvement in echocardiographic parameters was powered by Group A rather than Group B which is in contrast to the findings in the present interim analysis of STRIVE HF. Similarly in patients with AF and a pre-existing indication for bradycardia pacing, Leclercq et al. compared TriV pacing with BiV pacing in 34 patients who were implanted using two LV leads and one RV lead.[188] After a 3-month run-in period of BiV pacing, patients were then randomised to receive either three months of TriV pacing followed by three months of BiV pacing or three months of BiV pacing followed by three months of TriV stimulation and found a significant improvement in LV remodelling compared with conventional BiV pacing which is again in contrast to the findings of the present study.[188] Ginks et al. (2012) reported that multisite LV pacing increased the acute response rate to CRT in 16% of patients versus single-site pacing which was particularly beneficial in patients with posterolateral scar identified on CMR.[187] More recently, the V^3 trial randomised 84 patients deemed to be CRT non-responders

according to their clinical composite scores to continue with conventional BiV pacing or to receive an upgrade to TriV pacing with the addition of a second LV lead.[242] Although the V^3 trial reported that TriV pacing was feasible with a high implant success rate, the addition of a second LV lead in the CRT non-responder population did not result in any significant clinical benefit or any significant volumetric improvement on 2D echocardiography and was in fact associated with a significantly higher perioperative complication rate for procedure or system-related complications (infection, system explant, pneumothorax and hematoma) in 9/44 patients(20.4%).[242] The feasibility of TriV pacing was 82.1% in the present study which is similar to that reported in the V^3 trial of 80%,[242] confirming that TriV pacing is technically feasible in terms of both implanting and maintaining TriV pacing. The V^3 trial had a longer follow-up period (two years) compared to the present study (six months) and therefore was able to identify and report significantly higher complication rates in patients with triventricular pacing which was not found in the present study. However, this cannot be directly extrapolated to the present trial which involved *de novo* CRT-D or upgrade to CRT-D implantation compared to the V^3 trial which recruited a sicker cohort of CRT non-responders involving addition of an LV lead.

3.4.3 Limitations

The objective of STRIVE HF was to determine whether patients with LBBB and intermediate QRS prolongation 120-150ms (Class 1B indications for CRT) would benefit from TriV pacing. Therefore patients with LBBB and QRS duration >150ms (Class 1A indications for CRT) were excluded from the study based on previous work that suggested such patients with a high probability of a good response to BiV pacing (i.e.

patients with a broad LBBB) are unlikely to obtain further benefit from implanting an additional LV pacing lead.[187,190,191] It is unlikely that the study outcomes would have differed given this was a randomised control study with the control arm receiving conventional CRT with a single LV lead, however this was not evaluated in the present study given the trial design. In addition, only patients referred for CRT-D were included in the study as the TriV device with an internal Y-connector used in the study is not manufactured in a CRT-P version and therefore may have led to selection bias. Similarly, patients with pre-existing ICD devices undergoing upgrade to a CRT-D were not recruited unless they had a pre-existing and working DF-1 shock lead as required by the TriV device used in the study. Contrastingly, patients with a pre-existing bradycardia pacing system were able to be recruited providing they were planned for an upgrade to a CRT-D which may also have contributed to selection bias. The difficulties that were sometimes encountered with identifying two LV lead thresholds at the 6-month pacing check means that the number of patients TriV pacing at 6 months could in-fact have been higher, however, this would not have affected the volumetric or other clinical outcome results. There was no echocardiographic core laboratory used in STRIVE HF trial due to limited funding, therefore volumetric interrater and intrarater agreements were unable to be standardised, however, we do not believe this would have affected the study outcomes given all outcomes were negative with no trends towards significance apart from absolute change in 6MWT distance.

3.5 Conclusion

STRIVE HF was a prospective, multicentre randomised controlled trial specifically designed to assess feasibility and outcome benefits of TriV pacing in patients with LBBB and an intermediate QRS duration 120-150ms. This interim analysis shows that implantation of two LV leads carries a high success rate and TriV pacing appears to be feasible without significant complications at 6-month follow-up. However, there was no evidence that TriV pacing improves CRT response or has any clinical benefit to patients with LBBB and intermediate QRS prolongation. The completion of the STRIVE HF study is awaited before any final conclusions and recommendations to clinical practice are made.

Chapter 4: Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity

This chapter has been adapted from *Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity.* [40]

4.1 Introduction

Appropriate therapy occurs in one third of patients implanted with an ICD indicating better risk stratification of VA is needed.[208] Identifying VAs may also play an important role in identifying patients who may benefit from prophylactic VT ablation.

Cardiac magnetic resonance imaging with LGE is considered the non-invasive imaging reference standard for identifying ventricular scar with the presence and extent of LV scar predicting VA.[243,244] Small areas of ventricular scar that do not necessarily cause significant LV systolic dysfunction, may result in life-threatening VAs with CMR tissue characterization of scar core and grayzone tissue (scar penumbra) predicting VA in patients with ischemic cardiomyopathy (ICM).[245–248] In non-ischemic cardiomyopathy (NICM), diffuse myocardial fibrosis acts as a potential substrate for VA and we have previously shown that $T1^{-native}$ values predict appropriate ICD therapy [246,247] These techniques require a learning curve with specialized protocols for T1 mapping and signal intensity derived values for grayzone analysis. Furthermore, these scar assessment methods do not fully quantify tissue heterogeneity as they do not examine the entire array of pixels available from LGE imaging. Additionally, numerical simulation studies have shown spatial heterogeneity of fibrosis correlates directly with VA risk and is more evident as spatial size and degree of heterogeneity both increase.[249]

Quantitative texture analysis is a new technique that uses software formerly used and validated for the assessment and stratification of solid tumours.[250–252] Cardiac Magnetic Resonance Texture Analysis quantifies the entire distribution of pixel intensities within a region of ventricular scar from LGE imaging. The filtration-histogram technique highlights image features of a specified size, followed by histogram analysis of the filtered LGE image,[251] from which statistical parameters are derived including image entropy, a measure of disorder that characterizes image complexity by evaluating fibrosis heterogeneity. In essence, a set of completely white pixels would have an entropy value of zero but as the scar image becomes more complex, numerous different pixel values are detected and the entropy value increases enabling scar complexity evaluation. Our institution recently reported the use of CMR-TA in post-myocardial infarction patients with greater tissue heterogeneity being associated with a greater incidence of adverse outcomes.[253]

The study objective was therefore to determine whether scar heterogeneity, quantified by mean entropy, predicts appropriate ICD therapy. We hypothesized that higher mean entropy calculated from CMR-TA would predict appropriate ICD therapy in patients undergoing ICD implantation.

4.2 Methods

4.2.1 Study population

Consecutive patients undergoing primary and secondary prevention ICD implantation between May 2011-January 2013 were prospectively enrolled from two centers. We have previously assessed grayzone and T1 mapping indices to assess VAs in patients included in this cohort.[246] All study participants were on optimal heart failure and/or antiarrhythmic therapy and underwent coronary angiography and CMR assessment prior to device implantation. ICM was defined by standard criteria (prior myocardial infarction, presence of any epicardial coronary artery stenosis >75% or coronary revascularization with a scar pattern consistent with myocardial infarction on CMR imaging). Absence of the above criteria were defined as NICM. Primary prevention was defined as ICD implantation to reduce sudden cardiac death (SCD) in at-risk individuals who had not yet experienced an aborted cardiac arrest or life-threatening arrhythmia. Secondary prevention was defined as ICD implantation in patients who already had experienced an aborted cardiac arrest or life-threatening arrhythmia. The study protocol was approved by the South East London Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

4.2.2 CMR protocol and analysis

We have previously described the CMR protocol.[246,247] In summary, CMR imaging was performed using a 1.5 Tesla (T) scanner with a 32-channel cardiac phased array surface coil (Philips Healthcare, Best, The Netherlands). Following a Look-Locker acquisition to

identify optimum inversion time, an inversion-recovery gradient-echo pulse sequence was used to acquire a stack of short axis slices 10-15 minutes after Gadobutrol 0.2mmol/kg body weight contrast injection (Bayer-Schering Pharma, Berlin, Germany) for LGE assessment from which scar indices were calculated. CMR-derived scar indices for 2 standard deviation (SD) method ($Scar^{-2SD}$), full-width half-maximum (FWHM) method ($Grayzone^{-2SD\text{-}FWHM}$) and T1 mapping have been described.[246,247,254] Scar and grayzone indices were indexed as percentage of the LV mass. Two independent CMR experts blinded to the study endpoint evaluated the LGE images separately and resolved any discrepancies mutually.

4.2.3 Cardiac Magnetic Resonance Tissue Analysis (CMR-TA)

Patients without visible scar were excluded from the study. All areas of visible scar throughout the short axis LV stack were manually segmented and analysed using TexRAD research software (TexRAD Ltd., Feedback PLC, Cambridge, UK). Manual segmentation was performed by a CMR-trained cardiologist blinded to patient identifiers and study endpoints. For interrater agreement, a second CMR-trained cardiologist performed manual segmentation blinded to the initial assessors' results. CMR-TA was performed as previously described with regions of interest drawn around all visible LGE, carefully incorporating the scar border and excluding surrounding myocardium.[253] A Laplacian of Gaussian band-pass filter was subsequently used to extract and augment features of different sizes based on the spatial scale filter (SSF) values from 2-6mm radius (SSF2-6) corresponding to fine, medium and coarse texture scales respectively (Figure 4-1) as previously described.[251,253] Quantification of scar texture with histogram analysis of pixel intensity was then performed, generating

statistical parameters including entropy. In this study, we evaluated whether mean entropy, calculated from a medium scar texture (SSF4), predicts appropriate ICD therapy in patients undergoing ICD implantation and compared the results to $T1^{-native}$, $Grayzone^{2SD\text{-}FWHM}$ and $scar^{-2SD}$.

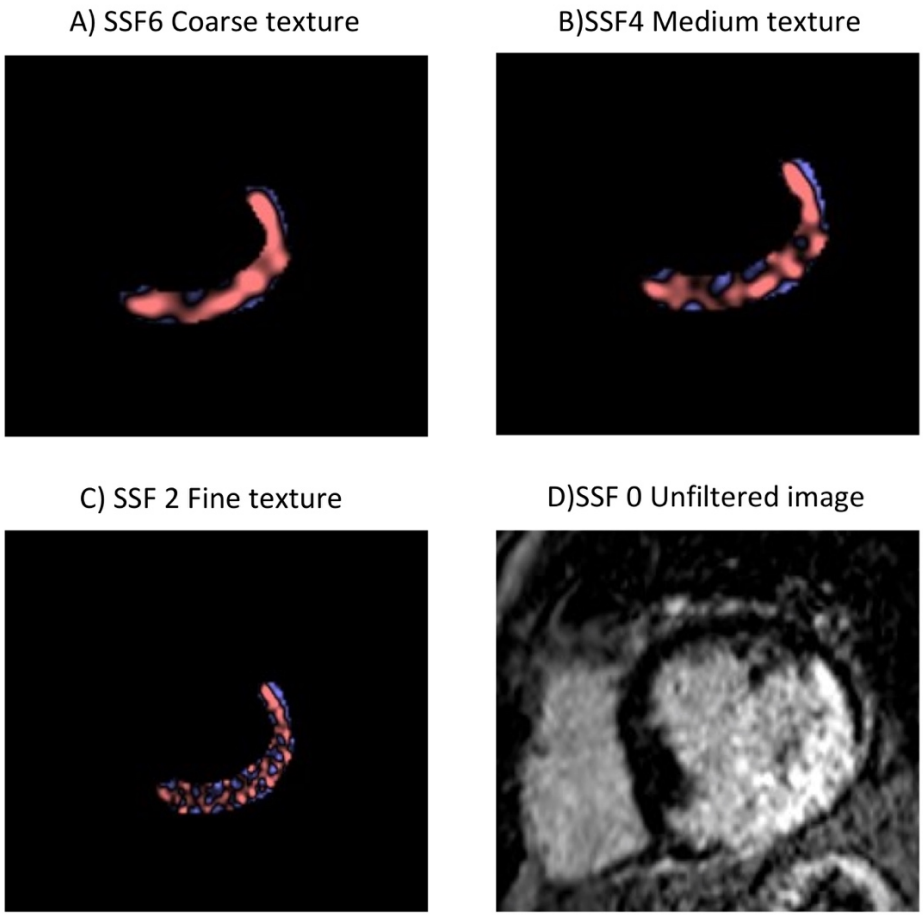


Figure 4-1: Scar texture examples generated from Laplacian filters applied to LGE images to extract and augment features of different sizes based on the spatial scaled filter values from 2-6mm radius (SSF2-6) corresponding to A) coarse, B) medium and C) fine texture scales respectively. D) corresponding unfiltered LGE image.

4.2.4 Follow-up and endpoint

All patients received an ICD or CRT-D. A standardized program for appropriate VA detection and ICD therapy with ATP or shock therapy was used as previously described.[246] VAs >170 beats/minute (detection count >16 intervals) were treated with ATP initially, then shock therapy for unsuccessful ATP. First-line shock therapy was used for VAs >210 beats/min (detection count 24/30 intervals). Patients were followed up at three-month intervals by experienced device physiologists who evaluated recorded events with an electrophysiologist, both blinded to the CMR data. The primary endpoint was delivery of appropriate ICD therapy for VT or ventricular fibrillation (VF) documented by the device.

4.2.5 Statistical analysis

Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean±1SD. Time to events are shown as median[interquartile range (IQR)]. Discrete demographic variables were compared using Fisher's exact test. Normally distributed data were compared with an independent samples t-test. Non-normally distributed data were compared using the Wilcoxon signed-rank test. The first episode of appropriate ICD therapy was considered the index event. Interrater agreement was evaluated using a Bland-Altman plot and linear regression analysis. Univariable and multivariable Cox proportional hazard regression models were performed to determine predictors of ICD therapy. Separate multivariable models were used to avoid multicollinearity where variables correlated. To avoid overfitting,

multivariable models were restricted to five variables for the entire cohort analysis and three variables when assessing cardiomyopathy groups independently. Statistically significant variables at univariable analysis and important clinical covariates were used as the basis for multivariable analysis ($p \leq 0.05$ was considered statistically significant). Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy and per 10 millisecond increase in T1-native value). Receiver operating characteristic (ROC) curves for mean entropy were plotted to identify optimal threshold values determined by Youden's index and retrospectively used to dichotomize patients into high and low mean entropy groups determined by whether they had met the primary endpoint. Kaplan–Meier survival curves were subsequently plotted to evaluate cumulative event rates and survival distributions. Statistical analysis was performed using Statistical Package for Social Sciences, Macintosh V24.0.0.1(2017). Armonk, NY:IBM Corporation.

4.3 Results

A total of 114 patients underwent CMR-TA, 70 (61.4%) with ICM and 44 (38.6%) with NICM. In the NICM cohort, aetiologies were 41/44 (93.2%) idiopathic dilated cardiomyopathy (DCM), 2/44 (4.5%) hypertrophic cardiomyopathy and 1/44 (2.3%) sarcoidosis. Primary prevention ICD implantation occurred in 78/114 (68.4%) patients. Demographics are presented in Table 4-1. Patients with ICM were older (67.1±10.2 vs. 58.6±15.3 years, *P*=0.005) with a significantly greater number of patients with LV ejection fractions (LVEF) ≤35% (84.3% vs. 63.6%, *P*=0.014). Mean entropy was significantly higher in the ICM group (5.7±0.7 vs. 5.5±0.7, *P*=0.045). The ICM group also had significantly higher scar index values of regional fibrosis with grayzone and scar core compared to the NICM group (Grayzone$^{-2SD\text{-}FWHM}$ 10.1±4.9 vs. 7.1±6.0, *P*=0.002; Scar^{-2SD} 25.0±9.1 vs. 16.2±13.3, *P*<0.001; Scar^{-FWHM} 15.0±6.5 vs. 9.0±8.6, *P*<0.001). Both groups were balanced for gender and other comorbidities (Table 4-1).

4.3.1 Primary endpoint

During median follow-up of 955[IQR 691-1185] days, 33 (28.9%) patients met the primary endpoint. Median time to first appropriate ICD therapy was 329[116-529] days for the entire cohort and similar between ICM and NICM groups (340[101-515] vs. 329[204-532], *P*=0.824). Of the 33 patients meeting the primary endpoint, 15/33 (45.5%) were treated for VF and 18/33 (54.5%) were treated for VT. A total of 16/33 (48.5%) received successful ATP and 17/33 (51.5%) patients received appropriate and successful shock therapy. The cumulative event rate for the primary endpoint was

similar between ICM and NICM groups (18/70, 25.7% vs. 15/44, 34.1%, *P*=0.398). A greater proportion of appropriate ICD therapy occurred in the secondary vs. primary prevention indication group (15/36, 41.7% vs. 18/78, 23.1%, *P*=0.049).

Table 4-1: Patient demographics according to heart failure aetiology

Demographics	**ICM (n=70)**	**NICM (n=44)**	**Total (n=114)**	***P* value**
Mean age (years±SD)	67.1±10.2	58.6±15.3	63.9±13.1	0.005
Male	56(80.0%)	34(77.3%)	90(78.9%)	0.815
Diabetes mellitus	13(18.6%)	6(13.6%)	19(16.7%)	0.609
Hypertension	25(35.7%)	14(31.8%)	39(34.2%)	0.691
Atrial fibrillation	14(20.0%)	14(31.8%)	28(24.6%)	0.183
Renal function (eGFR mL/min/1.73m^2)	66.8±20.4	69.9±17.0	68.0±19.1	0.406
Secondary prevention	23(32.9%)	13(29.5%)	36(31.6%)	0.837
CRT device	37(52.9%)	25(56.8%)	62(54.4%)	0.704
QRS>120ms	27(42.9%)	22(55.0%)	49(47.6%)	0.312
CMR LVEF≤35%	59(84.3%)	28(63.6%)	87(76.3%)	0.014
Mean Entropy	5.7±0.7	5.5±0.7	5.6±0.7	0.045
$T1^{-native}$	1051±73.1	1079±76.7	1062±75.3	0.079
$Grayzone^{-2SD-FWHM}$	10.1±4.9	7.1±6.0	8.9±5.5	0.002
$Scar^{-2SD}$	25.0±9.1	16.2±13.3	21.6±11.7	<0.001
$Scar^{-FWHM}$	15.0±6.5	9.0±8.6	12.7±7.9	<0.001

Patients were dichotomized into ischemic (n=70) and non-ischemic (n=44) cardiomyopathy groups.

4.3.2 Predictors of appropriate ICD therapy in the entire cohort

Univariable analysis showed secondary prevention, mean entropy, $T1^{-native}$, $Grayzone^{-2SD\text{-}FWHM}$ and $Scar^{-2SD}$ were associated with appropriate ICD therapy (Table 4-2). Avoiding multicollinearity, separate multivariable analyses showed mean entropy, $T1^{-native}$, $Grayzone^{-2SD\text{-}FWHM}$ and $Scar^{-2SD}$ remained independent predictors of appropriate ICD therapy (Figure 4-2). An interaction term of 'mean entropy x cardiomyopathy group' was added to the multivariable Cox proportional hazard regression model, however this was not statistically significant (HR 1.219, 95% CI 0.390-3.803, *P*=0.734) indicating no interaction between these co-variates.

Table 4-2: Univariable analysis of appropriate ICD therapy for the entire cohort

Variable	Hazard Ratio	95% CI	*P* value
Age	0.977	0.953-1.001	0.061
Male gender	2.046	0.719-5.822	0.180
Hypertension	0.565	0.285-1.123	0.103
Atrial fibrillation	0.658	0.313-1.382	0.269
Secondary prevention	**2.207**	**1.109-4.391**	**0.024**
QRS>120 milliseconds	1.075	0.518-2.229	0.847
CMR LVEF $\leq$ 35%	1.508	0.623-3.654	0.363
Renal function (eGFR 60 mL/min/1.73m^2)	1.010	0.993-1.027	0.254
CRT device	1.011	0.509-2.006	0.976
History of myocardial infarction	0.808	0.402-1.625	0.550
ICM	0.724	0.364-1.437	0.355
Bystander CAD	1.021	0.311-3.347	0.973
Mean Entropy	**1.687**	**1.028-2.769**	**0.038**
T1$^{-native}$	**1.008**	**1.003-1.013**	**0.002**
Grayzone$^{-2SD-FWHM}$	**1.100**	**1.039-1.165**	**0.001**
Scar^{-2SD}	**1.039**	**1.008-1.072**	**0.013**
Scar^{-FWHM}	1.034	0.991-1.077	0.121

Univariable Cox proportional hazard regression to determine variables associated with appropriate ICD therapy for the entire cohort (n=114). Mean entropy is presented as a continuous variable. Variables found to be statistically significant at univariable analysis as well as important clinical covariates were used as the basis for multivariable analysis. A value of p≤0.05 was considered to be statistically significant. All reported associations are presented as hazard ratios with corresponding 95% confidence intervals.

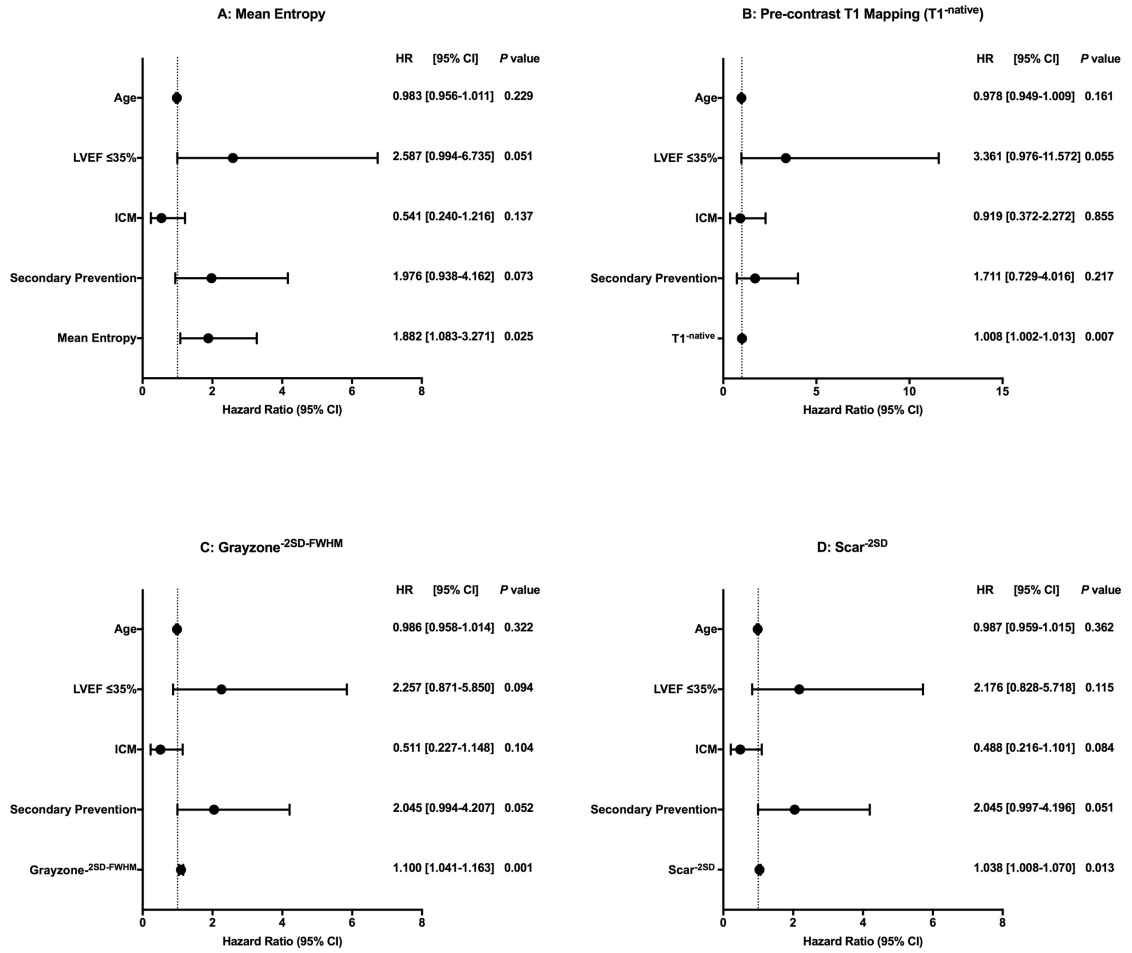


Figure 4-2: Separate multivariable Cox regression analyses to determine independent predictors of appropriate ICD therapy for the entire cohort (n=114) using different scar indices (A: mean entropy, B: T1-native, C: Grayzone-2SD-FWHM, D: Scar-2SD

Separate multivariable models were used to avoid multicollinearity. All reported associations are presented as hazard ratios with corresponding 95% confidence intervals. Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy and per 10 millisecond increase in T1-native value). P≤0.05 was considered statistically significant.

4.3.3 Predictors of appropriate ICD therapy in the ICM and NICM groups

For the ICM group, univariable analysis showed mean entropy was associated with the primary endpoint (Table 4-3) and remained an independent predictor of appropriate ICD therapy when tested in a multivariable model including age and LVEF≤35% (Figure 4-3). For the NICM group, univariable analysis showed only $T1^{-native}$ was associated with the primary endpoint (Table 4-4) and remained an independent predictor of appropriate ICD therapy when tested in a multivariable model including age and LVEF≤ 35% (Figure 4-4). Mean entropy was not associated with the primary outcome in the NICM group at univariable analysis (Figure 4-3).

Table 4-3: Univariable analysis of appropriate ICD therapy for the ICM group

Variable	Hazard Ratio	95% C.I.	*P* value
Age	0.974	0.929-1.022	0.282
Male gender	1.984	0.456-8.633	0.361
Hypertension	0.431	0.170-1.094	0.076
Atrial fibrillation	0.550	0.196-1.545	0.257
Secondary prevention	2.090	0.817-5.346	0.124
QRS>120 milliseconds	0.876	0.317-2.419	0.799
CMR LVEF $\leq$ 35%	1.520	0.349-6.616	0.577
Renal function (eGFR 60 mL/min/1.73m^2)	1.004	0.982-1.026	0.724
CRT device	0.893	0.354-2.252	0.811
Mean Entropy	**2.143**	**1.088-4.221**	**0.027**
T1$^{-native}$	**1.008**	**1.001-1.015**	**0.025**
Grayzone$^{-2SD-FWHM}$	**1.125**	**1.047-1.208**	**0.001**
Scar^{-2SD}	**1.096**	**1.037-1.157**	**0.001**
Scar^{-FWHM}	**1.088**	**1.015-1.165**	**0.017**

Univariable Cox proportional hazard regression to determine variables associated with appropriate ICD therapy for all patients with ischaemic cardiomyopathy (n=70). Mean entropy is presented as a continuous variable. Variables found to be statistically significant at univariable analysis as well as important clinical covariates were used as the basis for multivariable analysis. A value of $p \leq 0.05$ was considered to be statistically significant. All reported associations are presented as hazard ratios with corresponding 95% confidence intervals.

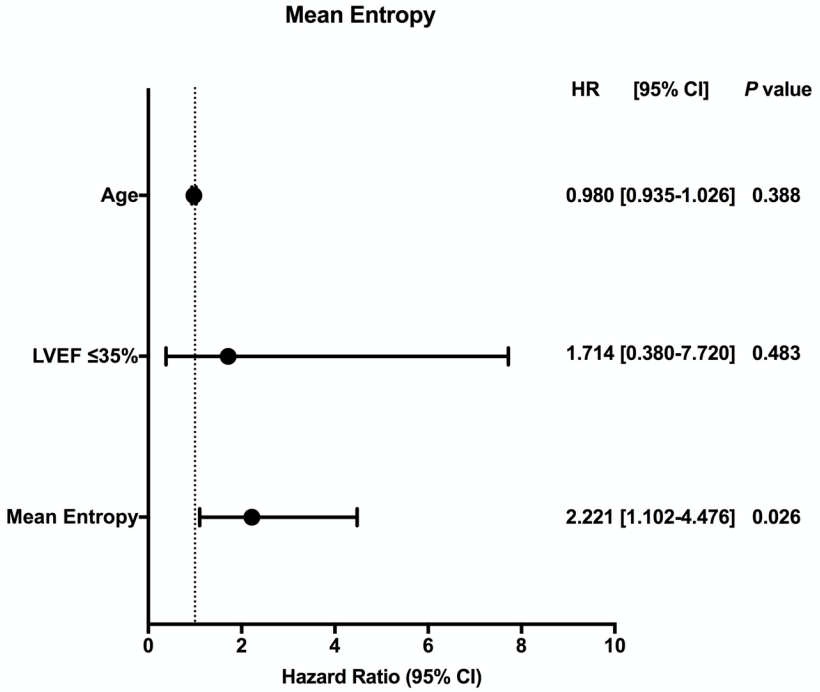


Figure 4-3: Multivariable Cox regression analysis to determine independent predictors of appropriate ICD therapy for patients with ischemic cardiomyopathy (n=70).

All reported associations are presented as hazard ratios with corresponding 95% confidence intervals. Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy). $P \leq 0.05$ was considered statistically significant.

Table 4-4: Univariable analysis of appropriate ICD therapy for the NICM group

Variable	Hazard Ratio	95% C.I.	*P* value
Age	0.980	0.949-1.013	0.238
Male gender	2.274	0.512-10.093	0.280
Hypertension	0.714	0.243-2.098	0.540
Atrial fibrillation	0.851	0.291-2.491	0.768
Secondary prevention	2.427	0.876-6.724	0.088
QRS>120 milliseconds	1.245	0.407-3.810	0.700
CMR LVEF $\leq$ 35%	1.865	0.593-5.867	0.286
Renal function (eGFR 60 mL/min/1.73m^2)	1.018	0.990-1.046	0.212
CRT device	1.163	0.414-3.271	0.774
Bystander CAD	0.932	0.263-3.308	0.914
Mean Entropy	1.434	0.637-3.226	0.384
$T1^{-native}$	1.009	1.001-1.017	0.033
$Grayzone^{-2SD-FWHM}$	1.075	1.000-1.155	0.051
$Scar^{-2SD}$	1.023	0.988-1.059	0.195
$Scar^{-FWHM}$	1.017	0.965-1.072	0.523

Univariable Cox proportional hazard regression to determine variables associated with appropriate ICD therapy for all patients with non-ischaemic cardiomyopathy (n=44). Mean entropy and $T1^{-native}$ values are presented as a continuous variable. Variables found to be statistically significant at univariable analysis as well as important clinical covariates were used as the basis for multivariable analysis. A value of $p \leq 0.05$ was considered to be statistically significant. All reported associations are presented as hazard ratios with corresponding 95% confidence intervals.

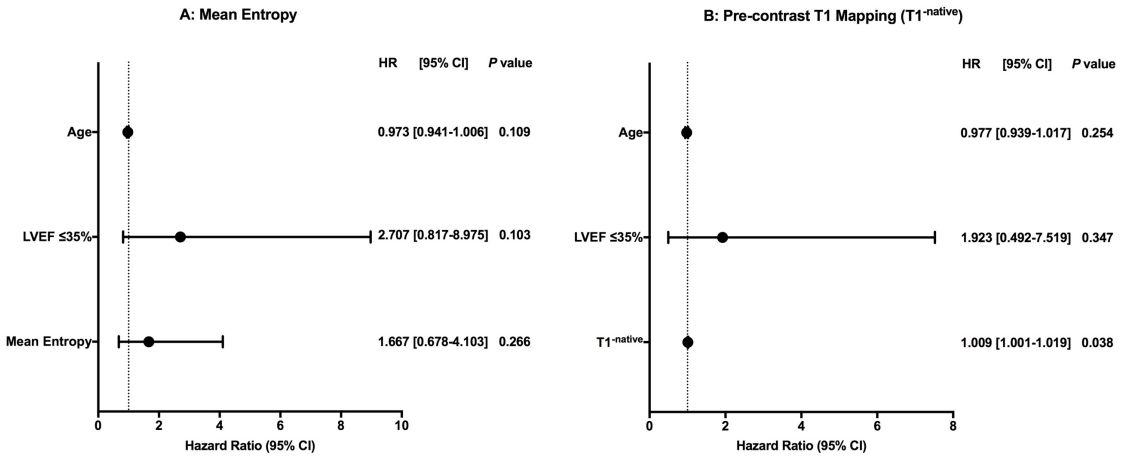


Figure 4-4: Multivariable Cox regression analyses to determine independent predictors of appropriate ICD therapy for patients with non-ischemic cardiomyopathy (n=44) using different scar indices (A: mean entropy, B: T1-native).

Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy and per 10 millisecond increase in T1-native value). $P \leq 0.05$ was considered statistically significant. All reported associations are presented as hazard ratios with corresponding 95% confidence intervals.

4.3.4 Survival analysis

Kaplan-Meier survival analysis (Figure 4-5) demonstrated that the time until first appropriate ICD therapy was significantly shorter in the high mean entropy group with an optimized cut off of >5.465 (Log rank 8.9, *P*=0.003). Furthermore, in the high mean entropy group there were significantly higher rates of appropriate ICD therapy over time with more than 40% having appropriate ICD therapy compared to the low mean entropy group with <20% appropriate ICD therapy.

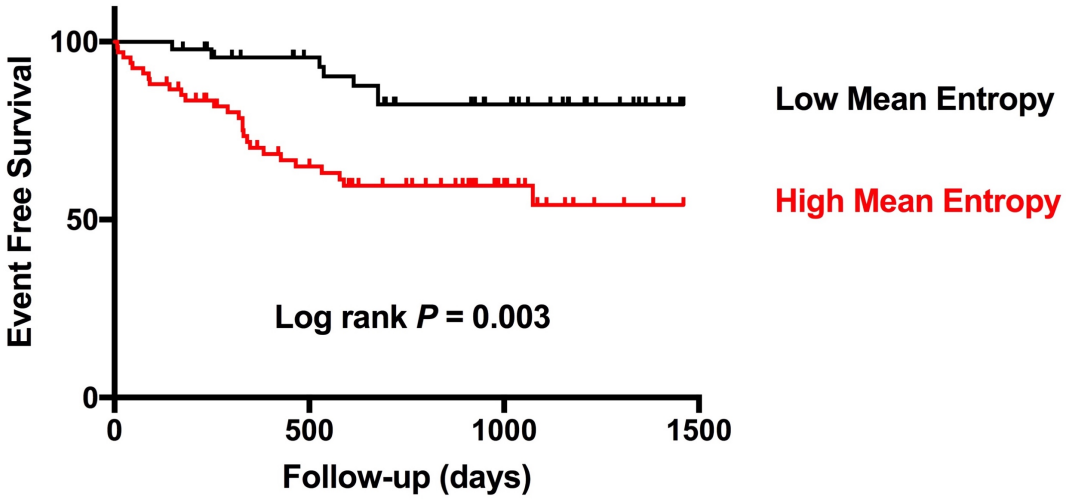


Figure 4-5: Kaplan-Meier survival analysis showing difference in event-free survival when patients are stratified according to mean entropy for the entire cohort.

Thresholds used to stratify patients are optimized cut-off values derived from Youden's index (high mean entropy >5.465, low mean entropy ≤5.465).

4.3.5 Reproducibility of mean entropy

The Bland-Altman plot in Figure 4-6 shows the absolute difference in mean entropy values calculated by histogram analysis of the segmented scar regions of 15 randomly selected patients (8 with ICM and 7 with NICM) by two independent assessors. For each patient, both CMR-trained cardiologists segmented total visible scar throughout the left ventricle. CMR-TA software automatically generated scar textures of each segmented scar region from which histogram analysis was performed to calculate entropy values for each segmented region. The mean of the entropy values from each segmented scar region were taken as the mean entropy value for each patient. The mean interrater difference for mean entropy was 0.0067 (limits of agreement -1.89 to 1.90) and displayed on a Bland-Altman plot (Figure 4-6). Linear regression also showed no statistical interrater difference (*P*=0.516, 95%CI -0.614-1.162). We have previously reported on the reproducibility of our T1 mapping method.[246,247]

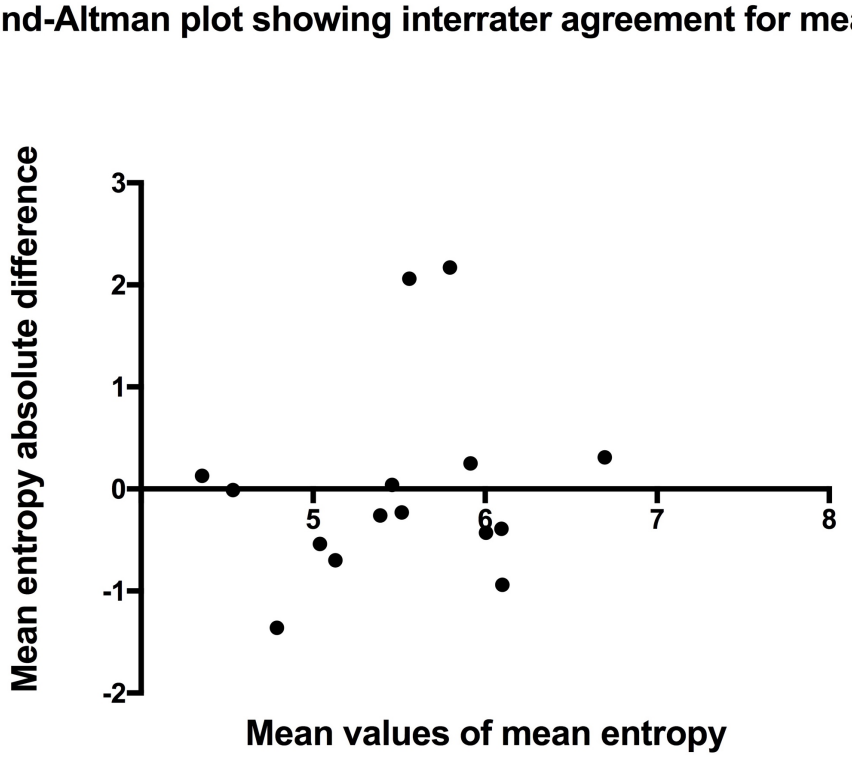


Figure 4-6: Bland-Altman plot showing absolute difference in mean entropy values calculated by histogram analysis of segmented scar regions from 15 randomly selected patients (ICM n=8 and NICM n=7) by two independent assessors.

For each patient, both CMR-trained cardiologists segmented total visible scar throughout the left ventricle. CMR texture analysis software automatically generated scar textures of each of the segmented scar regions from which histogram analysis was performed to calculate entropy values for each segmented region. The mean of the entropy values from each segmented scar region were taken as the mean entropy for each patient. The mean interrater difference for mean entropy was 0.0067 (limits of agreement -1.89 to 1.90).

4.4 Discussion

4.4.1 CMR Texture Analysis

Our novel findings demonstrate scar heterogeneity, quantified by mean entropy, is an independent predictor of appropriate ICD therapy in a mixed cardiomyopathy cohort (HR 1.882, 95% CI 1.083-3.271, *P*=0.025). In addition, $T1^{-native}$, $Scar^{-2SD}$ and $Grayzone^{-2SD-FWHM}$ were independent predictors of appropriate ICD therapy in the mixed cohort when tested in separate multivariable models.

4.4.2 CMR Texture Analysis in the ICM and NICM groups

In the ICM group, mean entropy remained an independent predictor of appropriate ICD therapy. The key strength of CMR-TA is in identifying subtle tissue heterogeneity by filtering out image noise and accentuating key features of LGE, thereby adding a layer of reproducibility and robustness in calculating mean entropy. Mean entropy is likely to be more reproducible than T1 mapping as T1 indices vary between different CMR scanners and magnet strengths. Only a standard white blood LGE sequence is required for CMR-TA and segmenting total visible scar has a short learning curve which could be automated in the future.

In the NICM group, there was no significant association between mean entropy and appropriate ICD therapy. This may be due to mechanistic differences in arrhythmogenesis between patients with regional ischemic scar in the ICM group versus patchy mid-wall fibrosis in the NICM group. Patients with NICM typically have a much

more diffuse pattern of fibrosis that is sometimes clearly visible as patchy mid-wall LGE. Only patients with visible scar were included in the study for both ICM and NICM groups to allow for this type of scar segmentation and evaluation. The fact that $T1^{-native}$ values outside of visible scar predict appropriate ICD therapy in the NICM group and mean entropy calculated from scar textures does not, suggests that diffuse interstitial fibrosis is likely to be more important in SCD risk stratification than focal patchy scar in the NICM population.[247,255] It therefore may be that performing entropy calculations in the NICM group is better served by not using a post-processing filtration method to generate scar textures and that using a total myocardium segmentation approach of unfiltered/raw LGE images is more appropriate as suggested by Muthalaly et al.[256] This alternative assessment of entropy in NICM patients by Muthalaly et al. may therefore be measuring diffuse scar burden compared to our technique that measures focal scar complexity and may also reflect that diffuse fibrosis in the NICM group is too small and interspersed to be detected using the filtration-histogram CMR-TA method. However, larger randomised multicentre trials are needed to evaluate this hypothesis further and correlate to histopathologic specimens.

4.4.3 Comparison with previous studies

Muthalaly et al. (2018) recently reported their findings of LV entropy as a measure of heterogeneity and found it was a predictor of arrhythmic events in 130 patients with DCM undergoing ICD implantation.[256] This is in contrast with the findings from the present study which did not identify mean entropy as a predictor of ICD events in the NICM group and may be explained by several methodological differences and differing baseline characteristics. Only 14% of patients experienced arrhythmic events in their

study compared to the NICM group in the present study where 34% of patients had appropriate ICD therapy indicating a higher risk NICM cohort over a shorter median follow-up (955[IQR 691-1185] days vs. 1168 days[IQR 1898 days]). Compared to our NICM group of 44 patients (n=41/44 with DCM) all with visible mid-wall fibrosis, only 56.9% of patients had visible LGE in Muthalaly et al.'s study. Furthermore, whilst Muthalaly et al. used the same formula to calculate entropy, they did not perform CMR-TA to filter out image noise and accentuate key image features of a specified size prior to entropy calculation and thus calculated entropy on raw unfiltered LGE images. In addition, they employed manual segmentation of total LV myocardium compared to our technique of total scar segmentation. It is therefore difficult to draw direct comparisons due to significantly different segmentation and entropy assessment methods even though mean LV entropy values were similar in Muthalaly et al. vs. the present study (5.6$\pm$0.7 vs. 5.5$\pm$0.7). There is no standardized method for scar segmentation to derive entropy, although in the ICM population, segmenting all visible scar or a selection of visible scar seems appropriate. The main challenge lies in quantifying heterogeneity of diffuse scar seen in NICM cohorts. We have demonstrated in this and previous studies,[246,247] that $T1^{-native}$ values derived from the mid septum outside of visible scar are predictive of appropriate ICD therapy in NICM supporting the use of $T1^{-native}$ values as an inherent tissue-specific index that is effective in differentiating healthy myocardium from diffusely diseased tissue.

4.4.4 Predictors of appropriate ICD therapy and clinical translation

We performed CMR-TA by segmenting visible scar and applying a spatial scale filter to identify subtle scar features, particularly in the ICM population, and should therefore

have greater robustness and stronger predictive value than other quantitative assessment methods of LV scar heterogeneity. We included patients with secondary prevention ICD indication and only patients with visible scar, and the predictive value of mean entropy is therefore likely to be robust in this already high-risk group. Mean entropy provides a more sophisticated method of quantifying scar heterogeneity than $T1^{-native}$, scar core and grayzone indices, and is reproducible and easier to perform, particularly for the ICM group. Additionally, our technique of careful scar segmentation included the scar border, allowing the filtration step to enhance scar texture heterogeneity by filtering out image noise and avoid inadvertent inclusion of 'healthy' myocardium thereby strengthening the reproducibility and robustness of the CMR-TA technique. Figure 4-7 compares the scar textures and unfiltered LGE images of a high mean entropy patient (A) who met the primary endpoint and a low mean entropy patient (B) who did not have ICD therapy. Moreover, CMR-TA has potential use in identifying patients that remain at high risk of VA and may guide prophylactic VT ablation in the ICM cohort. Its use in the NICM population is less clear and further larger multicentre studies are warranted.

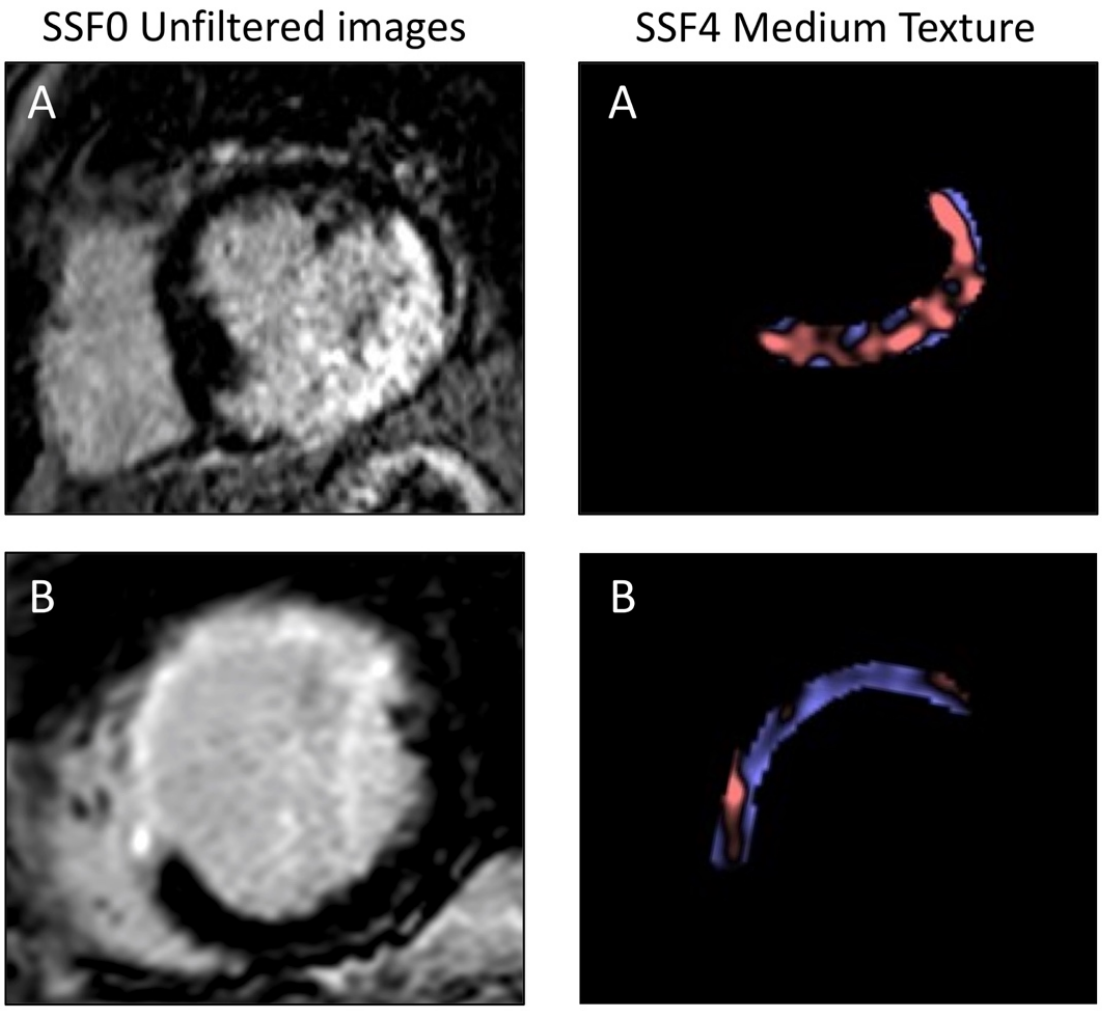


Figure 4-7: Visual comparison of unfiltered LGE images (left) and medium scar textures (right) of a high mean entropy patient (A) who met the primary endpoint and a low mean entropy patient (B) who did not receive ICD therapy.

A) Patient with ICM, LVEF≤35%, primary prevention ICD, transmural scar and high mean entropy (6.32) who received appropriate ICD therapy 319 days post ICD implantation.

B) Patient with ICM, LVEF≤35%, primary prevention ICD, transmural scar and low mean entropy (4.39) who did not receive appropriate ICD therapy during the study period.

Risk stratification of arrhythmic SCD is complex and multiple information from historical factors, biomarkers, autonomic parameters, surface ECG abnormalities (QT variability, T-wave alternans, T-wave oscillations), invasive EP studies, intracardiac electrograms, provocation testing and cardiac imaging (LVEF, ventricular scar assessment) have proven important although none offer 100% sensitivity.[213] Formal risk stratification tools will inevitably need to incorporate multiple modalities as it is unlikely any single measure will have sufficient discrimination to be used in isolation and the individual risk can markedly change over time suggesting static assessment is insufficient for accurate long-term risk stratification.

Scar texture analysis in the present study is the key distinguishing technique compared to other risk stratification tools which is considered more sensitive in identifying subtle tissue heterogeneity by filtering out image noise and accentuating key features of LGE, thereby adding a layer of reproducibility and robustness when calculating mean entropy. However, it differs from non-imaging risk stratification tools since scar is considered relatively 'fixed' and the electrical properties of scar undoubtedly evolve over time which may be more readily assessed using non-imaging modalities. LVEF as a single risk stratification tool is inadequate, mainly because it is a potent predictor of overall mortality and non-SCD and this significantly limits its specificity as a predictor for arrhythmic SCD.[213] Combining CMR-TA with LVEF<35% would almost certainly improve the specificity of using global LV systolic function, which on its own is only a crude marker of overall scar burden which does not account for scar heterogeneity.

4.4.5 Limitations

Our findings are subject to the inherent limitations of non-randomized controlled studies. The rate or morphology of VT in those receiving appropriate ICD therapy was not captured in the database which may have provided scope for a subanalysis to evaluate the differences in the type of VT requiring ATP or shock therapy. Additionally, use of appropriate ICD therapy as a surrogate endpoint does not necessarily parallel sudden arrhythmic death. Right ventricular scar was not evaluated which may contribute to the overall scar burden and arrhythmic substrate. Patients without scar were excluded to assess the predictive value of CMR-TA in a higher-risk population and is therefore not entirely representative of all cardiomyopathy patients. A potential limitation of our method in segmenting visible patchy scar for the NICM group is reproducibility. Furthermore, we recognize that inversion times, timing of LGE acquisition and additional imaging factors are unknown and require assessment. We used a standardized device therapy protocol mirroring our institutions guidelines when the study commenced. The Reduction in Inappropriate Therapy and Mortality through ICD Programming (MADIT-RIT) study later demonstrated optimized ICD programming by reducing ICD therapy which may potentially have reduced the event rate of this study.[192] Nevertheless, by standardizing ICD programming in our cohort, it is unlikely that device programming would have introduced any systemic bias in the associations studied.

4.5 Conclusion

Our novel findings demonstrate that scar heterogeneity, quantified by mean entropy using CMR-TA, was an independent predictor of appropriate ICD therapy in the mixed cardiomyopathy cohort as well as in the ICM group, suggesting a potential role for CMR-TA in predicting VA and risk-stratifying patients for ICD implantation.

Chapter 5: High mean entropy is associated with anti-tachycardia pacing failure in patients receiving ICD therapy: Insights using cardiac magnetic resonance texture analysis of scar heterogeneity and *in silico* computer modelling

This chapter has recently been submitted for publication in a peer reviewed journal

5.1 Introduction

Implantable cardioverter-defibrillators reduce mortality from VAs but are associated with complications including inappropriate shocks.[61,200] Mortality rates are higher in patients receiving ICD shock therapy[192,193,257,258] and may lead to heart failure progression.[194] A recent large meta-analysis including almost 200,000 patients demonstrated mortality was greater for appropriate compared to inappropriate shock therapy but both were associated with reduced survival with multiple shocks predicting worse outcomes.[193,207] Anti-tachycardia pacing may terminate VT avoiding shock therapy and represents an effective treatment of some but not all VA.[259] ATP has been shown to reduce unnecessary shocks and inappropriate shocks[192] and is therefore important in preserving ICD battery longevity and reducing the psychological impact of ICD shocks.[260] Furthermore, Sweeney et al. demonstrated ATP failure with subsequent ICD shocks was 18 times higher in patients who died at follow-up suggesting failed ATP therapy may be a marker of substrate severity.[207,261] Predicting patients more likely to have failed ATP and require shock therapy may therefore be of significant benefit in pre-counselling patients, ICD selection and programming. Quantifying microchannels within surviving areas of scar tissue (responsible for re-entrant VA) may be possible using cardiac magnetic resonance texture analysis (CMR-TA) to quantify scar heterogeneity from LGE imaging.[40] We previously demonstrated mean entropy, calculated using CMR-TA, predicts appropriate ICD therapy in patients undergoing ICD implantation.[40] In this current work, we hypothesized that scar heterogeneity (mean entropy) would be higher in patients that received appropriate ICD shock therapy compared to those that received

successful ATP. We used scar heterogeneity analysis to predict ICD shock therapy by performing a sub-analysis on patients with mixed aetiology cardiomyopathy that received appropriate ICD therapy (ATP or shock therapy). Additionally, we hypothesized that scar heterogeneity would be higher in patients with failed ATP compared to those receiving successful ATP and used *in silico* modelling based on CMR-derived scar geometry to explore potential mechanisms why ATP might fail.

5.2 Methods

5.2.1 Study population

Between May 2011-January 2013, consecutive patients undergoing primary and secondary prevention ICD implantation were prospectively enrolled from two tertiary centers. We previously reported the utility of mean entropy to predict appropriate ICD therapy (combined ATP/shock therapy) in this cohort.[40] All patients had heart failure and/or antiarrhythmic therapies optimized and underwent coronary angiography and CMR assessment prior to device implantation. Standard criteria defined ischemic cardiomyopathy (ICM); prior myocardial infarction; epicardial coronary artery stenosis >75%; or coronary revascularization with a scar pattern consistent with myocardial infarction on CMR. Absence of these criteria defined non-ischemic cardiomyopathy NICM. Primary prevention was defined as ICD implantation to reduce SCD in at-risk individuals who had not yet experienced a life-threatening VA or aborted cardiac arrest. Secondary prevention implants were in those patients who had already experienced a life-threatening VA or aborted cardiac arrest. The study protocol was approved by the South East London Research Ethics Committee and conducted in accordance with the Declaration of Helsinki.

5.2.2 CMR protocol and analysis

Our CMR protocol has been previously detailed.[40,246,247] CMR imaging was performed using a 1.5 Tesla (T) scanner with a 32-channel cardiac phased array surface coil (Philips Healthcare, Best, The Netherlands). Following a look-locker acquisition to identify

optimum inversion time, an inversion-recovery gradient-echo pulse sequence was used to acquire a stack of short axis slices 10-15 minutes after Gadobutrol 0.2mmol/kg body weight contrast injection (Bayer-Schering Pharma, Berlin, Germany) for LGE assessment from which CMR-TA was performed. Two independent CMR experts blinded to the study endpoint evaluated the LGE images separately and resolved any discrepancies mutually.

5.2.3 Cardiac Magnetic Resonance Tissue Analysis (CMR-TA)

We have previously described our CMR-TA methodology.[40,253] Patients without visible scar were excluded from analysis. All areas of visible scar throughout the short axis LV stack were manually segmented and analysed using TexRAD research software (Feedback Medical LTD, Cambridge, UK). Manual segmentation was performed by a CMR-trained cardiologist blinded to patient identifiers and study endpoints. CMR-TA was performed as previously described with regions of interest drawn around all visible LGE, carefully incorporating scar borders and excluding surrounding myocardium.[40,253] CMR-TA was performed using a Laplacian of Gaussian band-pass filter to extract and augment image features corresponding to a medium scar texture (spatial scale filter of 4mm radius), from which histogram analysis of pixel intensity calculated mean entropy as previously described.[40,251,253]

5.2.4 Follow-up and primary endpoint

All patients underwent implantation of an ICD or CRT-D. A standardized program for appropriate VA detection and ICD therapy with ATP or shock therapy was used as previously described.[40,246,247] VAs >170 beats/minute (detection count >16 intervals)

were treated with ATP initially, then shock therapy for unsuccessful ATP. First-line shock therapy was used for VAs >210 beats/min (detection count 24/30 intervals). Patients were followed up at three-month intervals by experienced cardiac physiologists who evaluated recorded events with an electrophysiologist, both blinded to the CMR data.

A total of 114 patients underwent CMR-TA in the original study where the primary endpoint was delivery of appropriate ICD therapy. In the present study, we performed a retrospective sub-analysis of the 33 patients receiving appropriate ICD therapy and dichotomized patients into those that received appropriate ICD shock therapy versus successful ATP (without shock therapy) and evaluated whether mean entropy predicted ICD shock therapy. We also evaluated whether mean entropy values were higher in patients that received unsuccessful ATP (and required rescue shock therapy) versus those that received successful ATP.

5.2.5 Computer modelling of left ventricular scar

In silico computer modelling was performed to explore potential mechanistic explanations underlying the clinical findings using a simplified 2D finite element geometry representing an idealized scar with a protected diastolic isthmus with mesh resolution 200um (Figure 5-1A and D). The infarct region comprised two semi-circular segments representing necrotic scar, transcended by a 4mm wide conducting isthmus. The necrotic scar was set to be insulating with no-flux boundary conditions on the intracellular potential. Patchy fibrosis, of variable density, was included in the protected isthmus by randomly replacing myocytes by non-conducting fibrotic tissue. For each density (*dFib*), 10 different topologies, with slightly different (random) fibrosis

distributions were generated. Figure 5-1 shows one specific topology of fibrosis distribution for an isthmus containing 10%(A) and 50%(D) fibrosis. Tissue electrophysiology was represented by the monodomain model, with cellular dynamics represented by the ten Tusscher ventricular cell model.[262] Additional simulations with impaired excitability in the isthmus were conducted by reducing the maximum channel conductance of the fast sodium current (INa). Simulations were conducted using Cardiac Arrhythmia Research Package.[263] Tissue was stimulated *in silico* at a site proximal to the isthmus mouth (entry site of potential VT re-entry circuit), as shown in Figure 5-1B. Three steady-state stimuli were delivered at a basic cycle length of 500ms; followed by a premature stimulus at a coupling interval of 320ms delivered at the same location. The standard definition of Shannon entropy was used to define an effective entropy score within the isthmus region for the cases of differing fibrosis densities.

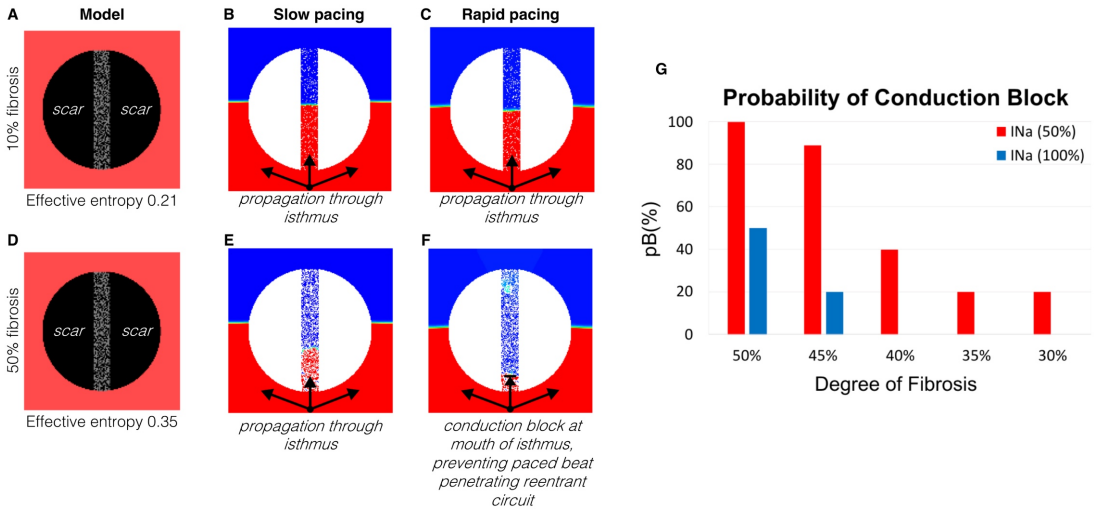


Figure 5-1: A specific topology example of fibrosis distribution for an isthmus containing 10%(A) and 50%(D) fibrosis.

The tissue was stimulated at a lower site proximal to the isthmus mouth(**B, C, E & F**). With 10% fibrosis within the isthmus, the paced activation wavefront is able to penetrate the isthmus at both slow(**B**) and fast(**C**) pacing rates. With 50% patchy fibrosis within the diastolic isthmus, activation at slow pacing rates is able to successfully penetrate the isthmus(**E**). At more rapid pacing rates, similar to VT cycle lengths, activation fails to penetrate the isthmus, blocking at its mouth(**F**). The probability of conduction blocking at the mouth of the isthmus was also seen to be a function of both the fibrosis density and also the excitability of the surviving tissue within the isthmus itself(**G**).

5.2.6 Statistical analysis

Discrete data are presented as n values with corresponding percentages in parentheses and continuous data as mean±1SD. Time to events are shown as median[interquartile range]. Discrete demographic variables were compared using Fisher's exact test. Normally distributed data were compared with an independent samples t-test. Non-normally distributed data were compared using Wilcoxon signed-rank testing. The first episode of appropriate ICD therapy defined the index event. Univariable and multivariable Cox proportional hazard regression models were performed to determine predictors of ICD shock therapy in patients receiving appropriate ICD therapy. Statistically significant variables at univariable analysis and important clinical covariates were used as the basis for multivariable analysis. To avoid overfitting, multivariable analysis was restricted to four variables. Hazard ratios for continuous variables represent the relative increased risk of endpoint per unit increase (e.g. per one unit increase in mean entropy). For all tests, $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences, Macintosh V 24.0.0.1 (2017). Armonk, NY, IBM Corporation.

5.3 Results

Of the 33 patients receiving appropriate ICD therapy, 17/33 (51.5%) received successful ICD shock therapy and 16/33 (48.5%) had successful ATP without requiring shocks. Median time to first appropriate ICD therapy was 329[116-529] days and was similar between those that received shock therapy vs. successful ATP therapy (290[89-357] vs. 388[143-593], p=0.154). Patients receiving appropriate ICD shock therapy had a significantly higher mean entropy value compared to those that had successful ATP only (6.1$\pm$0.5 vs. 5.5$\pm$0.7, p=0.037). Otherwise, patient characteristics were balanced between groups (Table 5-1). In the group that received successful shock therapy (n=17), 11 patients were treated for VF, 4 patients had failed ATP during charging for fast VT in the VF zone and a further 2 patients had failed ATP for VT at 190bpm and 210 bpm respectively. In the successful ATP group (n=16), VAs fell within the device VT zone.

Table 5-1: Baseline characteristics of patients receiving appropriate ICD therapy for VT/VF

Demographics	Received ICD Shock Therapy (n=17)	Successful ATP Therapy (n=16)	Combined ICD Therapy (n=33)	*p* value
Mean age (years±SD)	58.8±15.4	61.3±13.3	60.0±14.2	0.615
Male	14 (82.4%)	15 (93.8%)	29 (87.9%)	0.601
Diabetes mellitus	6 (35.3%)	2 (12.5%)	8 (24.2%)	0.225
Hypertension	9 (52.9%)	6 (37.5%)	15 (45.5%)	0.491
Atrial fibrillation	3 (17.6%)	7 (43.8%)	10 (30.3%)	0.141
Renal function (eGFR mL/min/1.73m^2)±SD	70.7±15.0	71.4±16.5	71.1±15.5	0.895
Ischemic cardiomyopathy	9 (52.9%)	9 (56.3%)	18 (54.5%)	1.000
Secondary prevention	10 (58.8%)	5 (31.3%)	15 (45.5%)	0.166
CRT device	9 (52.9%)	9 (56.3%)	18 (54.5%)	1.000
QRS>120ms	6 (46.2%)	8 (50.0%)	14 (48.3%)	1.000
CMR LVEF≤35%	13 (76.5%)	14 (87.5%)	27 (81.8%)	0.656
Mean Entropy	**6.1±0.5**	**5.5±0.7**	**5.8±0.7**	**0.037**

Patients receiving appropriate ICD therapy were divided into 'Required Shock Therapy' vs. 'Successful ATP' (no shock therapy) groups.

5.3.1 Predictors of ICD shock therapy

Univariable analysis showed only secondary prevention and mean entropy were associated with ICD shock therapy (Figure 5-2A). In a multivariable Cox proportional hazard regression model adjusting for significant and important clinical covariates (LV ejection fraction≤35%, ICM and secondary prevention), mean entropy was an independent predictor of ICD shock therapy (HR 3.50, 95% CI 1.29-9.54, *p*=0.014) as was secondary prevention (Figure 5-2B).

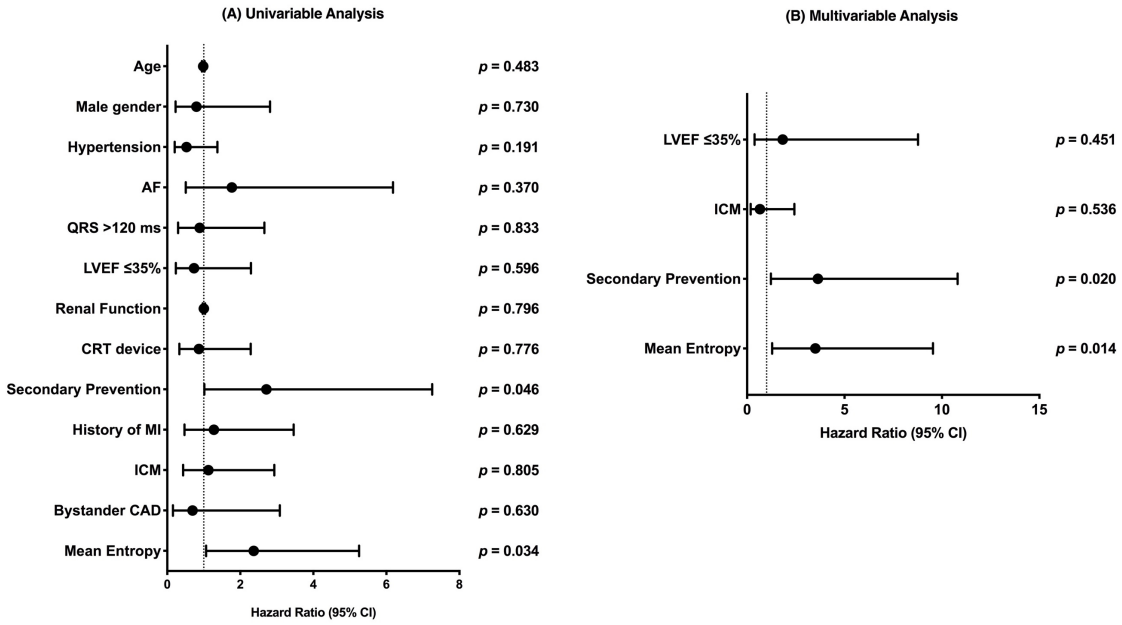


Figure 5-2: Univariable(A) and multivariable(B) Cox regression analyses to determine predictors of appropriate ICD shock therapy for patients (n=33) receiving appropriate ICD therapy (ATP or shock therapy).

5.3.2 Analysis of patients receiving ATP therapy

A total of 22 patients received initial ATP for their index event with 16/22 of these patients receiving successful ATP without requiring shock therapy. In the remaining 6 patients receiving failed ATP prior to the delivery of a successful ICD shock, mean entropy values were significantly higher compared to the successful ATP therapy group (6.3 ± 0.7 vs. 5.5 ± 0.7, p = 0.048) (Figure 5-3).

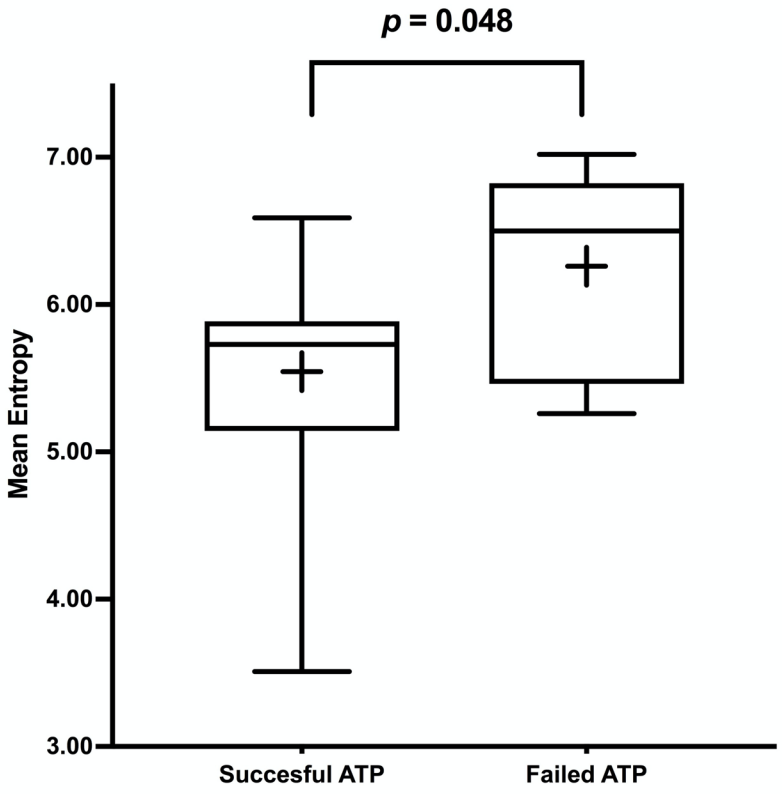


Figure 5-3: Box and whisker plots showing difference in 'mean entropy' between patients receiving successful ATP (no shock therapy) versus failed ATP (with rescue ICD shock).

+ = mean values of 'mean entropy'

Whiskers represent minimum and maximum absolute values of 'mean entropy

5.3.3 *In silico* modelling results

Computational simulations using the idealized infarct model were used to explore the clinical findings reported in Figure 5-3. We modelled how penetration of the re-entrant circuit was affected by the fibrotic tissue texture forming the protected isthmus. With a high degree of patchy fibrosis (50%) at slower pacing rates, the ATP pacing stimulus was able to successfully penetrate the isthmus (Figure 5-1E) albeit with reduced conduction velocity due to the tortuous course taken around the fibrotic regions.[264] At more rapid pacing rates (similar to VT cycle lengths) activation failed to penetrate the isthmus blocking at its mouth (Figure 5-1F). Notably with lower degrees of fibrosis (10% fibrosis within the isthmus) the paced activation wavefront was able to penetrate the isthmus at both slow (Figure 5-1B) and fast (Figure 5-1C) pacing rates. Shannon entropy was seen to peak at a level of 50% fibrosis (0.35) and fall to 0.21 for 10% fibrosis. The probability of conduction blocking at the mouth of the isthmus (corresponding with the entry site of VA) was also seen to be a function of excitability of the surviving tissue within the isthmus itself as well as fibrosis density, evidenced by the fact that as excitability was further impaired (by blocking INa) the probability of rate-dependent conduction block increased for all levels of fibrosis (Figure 5-1G).

5.4 Discussion

The results of the present study build upon our previous findings that mean entropy predicts appropriate ICD therapy (ATP or shock therapy) in patients with ICM or mixed aetiology cardiomyopathy undergoing ICD implantation.[40] To the best of our knowledge, this is the first analysis demonstrating the novel finding that scar heterogeneity, quantified by mean entropy, predicts ICD shock therapy compared to those receiving successful ATP. Furthermore, patients receiving unsuccessful ATP prior to the delivery of a successful ICD shock had significantly higher mean entropy values compared to those receiving successful ATP. This may be of particular clinical importance as it implies that a higher degree of scar heterogeneity (quantified by a higher mean entropy) may be associated with a more aggressive VA requiring shock therapy to terminate. Our *in silico* computer modelling provides a physiologically plausible mechanism to explain our results i.e. ATP failure in the presence of greater scar heterogeneity/fibrosis due to inability of the paced wavefront to propagate into the critical VT isthmus especially at more rapid pacing rates that are generally required for pace termination of VAs.

5.4.1 Potential mechanistic explanations for ATP failure

The reasons why higher mean entropy values predict a more aggressive VA requiring shock therapy may lie in the mechanistic differences in arrhythmogenesis between varying scar heterogeneity. A higher degree of myocardial scar tissue heterogeneity (higher mean entropy) may support a greater number of microchannels within scar facilitating micro re-entry circuits stable enough to form sustained VT or VF that do not

spontaneously abort and are more difficult to terminate with ATP requiring shock therapy to restore a stable heart rhythm. For ATP to be successful, the stimulus from the pacing electrode must successfully reach and penetrate the re-entrant circuit, closing-down the excitable gap.[265] The re-entrant circuit in sustained monomorphic VT often contains regions of patchy fibrosis, particularly in the diastolic isthmuses through which conduction is known to be impaired and which directly contribute to the arrhythmogenic substrate within the infarcted region. Thus, an important aspect of ATP success may be the ability of the paced wavefront to successfully propagate through patchy fibrosis within the isthmus, rendering it unexcitable when the re-entrant wave subsequently arrives. It has been shown that activation propagating through patchy fibrotic regions is susceptible to rate-dependent conduction block[264,266,267] with the wavefronts forced to take convoluted and tortuous pathways as they attempt to navigate their way through the patchy fibrotic regions, undergoing frequent rapid tissue expansions and experiencing significant electrotonic source-sink mismatches. Under steady-state conditions, tissue is sufficiently excitable to allow propagation to traverse such regions, albeit with a modulated conduction velocity.[268] However, during rapid pacing, tissue has impairing excitability, and thus electrotonic current source-sink mismatches may reach a threshold to prevent downstream activation, causing unidirectional block. Our computer modelling confirms that high levels of patchy fibrosis within the diastolic isthmus may be susceptible to rate-dependent unidirectional conduction block, which may play an important role in preventing an ATP-paced wavefront from penetrating the critical re-entrant channels within the infarct. Such a mechanism, driven by the electronic source-sink mismatch within the patchy fibrotic areas, may be exacerbated during compromised excitability at more rapid pacing rates. This is further supported by the augmentation of unidirectional block seen in situations

where excitability (via INa) was further directly compromised (Figure 5-1G). The amount of patchy fibrosis in a given region, as detected on an LGE image, is related to the level of entropy i.e. quantifying the degree of disorder, or how dissimilar a particular voxel is from its neighbour. Our *in silico* results suggest that regions with moderate patchy fibrosis levels (approximately 50%) have correspondingly higher entropy scores, compared to areas with lower fibrosis levels and provides a physiologically plausible mechanism for how infarcts with lower entropy scores may be more susceptible to successful ATP therapy whereas higher entropy regions may be more susceptible to ATP failure due to rate-dependent block.

5.4.2 Comparison with previous studies

Previous work on entropy and LGE is limited and has focussed on predicting appropriate ICD therapy (combined ATP or shock therapy). Androulakis et al. (2019) recently reported LV entropy as a measure of scar heterogeneity in post myocardial infarction patients and found that high entropy within scar was associated with ICD therapy (ATP or shock therapy for monomorphic VT or VF),[269] and in keeping with our previous findings.[40] Androulakis et al. found entropy of the entire LV myocardium was not a predictor of appropriate ICD therapy[269] in contrast to the findings of Muthalaly et al. (2018) who found it was a predictor of ICD therapy in 130 patients with DCM.[256] There is no standardized method for scar segmentation to derive entropy, although in the ICM population, segmenting all visible scar or a selection of visible scar seems appropriate. The findings from these recent studies suggest entropy of LV scar is useful in predicting ICD therapy in patients with ICM and entropy of the entire LV myocardium is useful in predicting ICD therapy in patients with NICM. Notably, Androulakis et al. identified that

high entropy of the entire LV myocardium was associated with mortality which may reflect a fibrosis pattern associated with adverse remodelling. Similarly, we have previously shown that $T1^{-native}$ values derived from the mid-septum outside of visible scar are predictive of appropriate ICD therapy in patients with NICM, supporting the use of $T1^{-native}$ values as an inherent tissue-specific index that is effective in differentiating healthy myocardium from diffusely diseased tissue.[40,246,247]

5.4.3 Clinical importance

Our work supports the hypothesis that patients with greater scar heterogeneity are at higher risk of malignant VAs that may ultimately require shock therapy to restore a stable heart rhythm. Furthermore, these findings substantiate previous computer modelling work that correlates the risk of VAs occurring with increasing heterogeneity of fibrosis.[249] Predicting which patients are at higher risk of receiving ICD shocks may be of significant benefit in counselling of ICD patients (helping to quantify the risk of shock therapy), device programming (using more aggressive ATP therapy in those likely to respond and less in those unlikely to respond) and also in device selection. Greater use of stand-alone subcutaneous ICDs (that are currently unable to deliver ATP) in patients unlikely to benefit or respond to ATP therapy may reduce the transvenous and mediastinal lead burden and subsequently reduce morbidity and mortality from systemic infection from indwelling leads in the circulation/mediastinum as well as from transvenous lead extraction, offering additional long-term economic benefits to healthcare systems. Another potential application is the development of novel lead technologies to deliver ATP. If, as our results suggest, ATP success is dependent on local myocardial properties/degree of fibrosis in relation to the stimulus location relative to

the re-entrant circuit, then delivery of ATP at potentially more favourable sites could be achieved with guided lead placement or multipolar leads that may offer an advantage over current techniques to deliver ATP. Since CMR-TA has the potential to identify patients at high risk of ATP failure and ICD shock therapy, it may also be useful in guiding prophylactic VT ablation in high-risk patients.

5.4.4 Limitations

Our findings are subject to the inherent limitations of non-randomized controlled studies. The morphology and cycle length of VT was not captured in the prospective database which may have provided further scope to evaluate differences in the type of VT responding to ATP versus shock therapy. Additionally, use of appropriate ICD therapy as a surrogate endpoint does not necessarily parallel sudden arrhythmic death. Right ventricular scar was not evaluated which may contribute to the overall scar burden and arrhythmic substrate. We used a standardized device therapy protocol according to our institutional guidelines when the study commenced. The MADIT-RIT study later demonstrated optimized ICD programming and may potentially have reduced the event rate of this study.[192] Nevertheless, by standardizing our ICD programming it is unlikely that device programming would have introduced any systemic bias in the associations studied, not least since in the group that received shock therapy the majority of patients had VF or failed ATP for a VA in the VF zone. We also acknowledge that there may be other potential mechanisms related to higher entropy in infarcted regions which could explain our findings that were not investigated with our computer modelling. Primarily, more complex scar (with additional bystander channels) could result in a more complex VT circuit that is harder to treat with bystander channels being responsible for VT

sustenance upon interaction with the paced ATP wavefront that could facilitate the degeneration into more complex VT/VF. Three-dimensional patient specific models of the subjects in this cohort to investigate VA circuits in relation to scar heterogeneity was not possible, due to the coarse out-of-plane resolution of the CMR data, meaning that full 3D realization of the infarct anatomy, including microscopic channels that might support VT, was not possible. Larger randomized multicentre trials are required to further evaluate our findings and correlation with histopathologic specimens would also be important to validate our findings which is beyond the scope of the current work.

5.5 Conclusion

A higher degree of scar heterogeneity, quantified by mean entropy, predicts ICD shock therapy in a high-risk group of ICD recipients. Our novel findings suggest that high mean entropy may be associated with more aggressive VAs unresponsive to ATP requiring shock therapy. Furthermore, our *in silico* computer modelling proposes a physiologically plausible mechanism to explain ATP failure in the presence of greater scar heterogeneity that may aid clinical decision making in patients more likely to benefit from early shock therapy.

Chapter 6: Conclusion

6.1 Summary of thesis objectives

The overall aim of this thesis was to explore novel ways to improve complex cardiac implantable electronic device therapy outcomes. Specifically, the main objectives were:

1. To explore the feasibility and potential benefit of using real-time cardiac CT image overlay guidance and multisite LV pacing as two distinct approaches to improve CRT response rates through optimal LV lead delivery.

2. To assess the benefit of quantifying scar heterogeneity, using cardiac MRI texture analysis (mean entropy), as a potential metric to predict appropriate ICD therapy and ATP failure and explore its potential role in ICD risk stratification.

6.2 Original contributions

The preceding body of work has successfully explored these primary objectives. In summary:

1. Chapter 2 has shown that real-time cardiac CT image overlay guidance for optimal LV lead placement in delivering CRT is safe and feasible. There were significant improvement in echocardiographic volumetric response outcomes at 6-months follow-up compared to baseline and the overall CRT response rate was high given the large number of patients with ICM and use of volumetric response as a hard endpoint. Larger, multicentre, randomised controlled studies are needed to evaluate whether real-time CT image overlay guidance is superior to standard care in patients undergoing an LV lead upgrade to CRT.

2. Chapter 3 was an interim analysis of the STRIVE HF study, a prospective, multicentre randomised controlled trial specifically designed to assess feasibility and outcome benefits of multisite LV (triventricular) pacing in patients with LBBB and an intermediate QRS duration 120-150ms. Whilst the results indicate that implantation of two LV leads and triventricular pacing is feasible without significant complication, there was no evidence that multisite LV pacing improves CRT response or has any clinical benefit to patients with LBBB and intermediate QRS prolongation. The completion of the STRIVE HF study is awaited before any final conclusions and recommendations to clinical practice are made.

3. Chapter 4 showed for the first time that scar heterogeneity, quantified by mean entropy using cardiac MRI texture analysis, was an independent predictor of appropriate ICD therapy in the mixed cardiomyopathy cohort and ICM-only group, suggesting a potential role in predicting ventricular arrhythmias and risk-stratifying patients for ICD implantation.

4. Chapter 5 also revealed novel findings that suggest lower scar heterogeneity, quantified by mean entropy using cardiac MRI texture analysis, is associated with successful ATP whereas higher scar heterogeneity is associated with more aggressive ventricular arrhythmias unresponsive to ATP requiring shock therapy.

6.3 Future work

Cardiac CT has the potential to identify areas of latest mechanical activation and guide LV lead implants into optimal pacing sites using real-time image overlay technology. Furthermore, if late iodine enhancement protocols for cardiac CT improve and match the reliability of scar imaging obtained from CMR imaging, then cardiac CT may in the future become the imaging modality of choice for both de novo and upgrade image guided CRT procedures. Larger, multicentre, randomised controlled studies are needed to evaluate whether real-time CT image overlay guidance is superior to standard care in patients undergoing an LV lead upgrade to CRT.

The completion of the STRIVE HF study is awaited, however, if the final results are similar to the ones presented in the interim analysis in Chapter 3, then it is unlikely that multisite LV pacing should be pursued in the future.

CMR texture analysis has the potential to be incorporated into an ICD risk stratification score. Larger randomized multicentre trials are required to further evaluate the potential value of quantifying scar heterogeneity, using cardiac MRI texture analysis (mean entropy), as a potential metric for ICD risk stratification. Furthermore, correlation with histopathologic specimens of LV myocardium would also be important in the future.

First author publications arising from thesis work and future work to publish

1. **Gould J et al.** Chronic Right Ventricular Pacing in the Heart Failure Population. Curr Heart Fail Rep 2018.

2. **Gould J et al.** Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity. Heart Rhythm Elsevier, 2019; 16:1242–1250.

3. Chapter 5 (**Gould et al.**) has recently been submitted for publication in a peer reviewed journal with the title High mean entropy is associated with anti-tachycardia pacing failure in patients receiving ICD therapy: Insights using cardiac magnetic resonance texture analysis of scar heterogeneity and in silico computer modelling.

4. Chapters 2 and 3 **(Gould et al.)** will be submitted for publication in a peer reviewed journal when further results are available.

First author conference presentations arising from thesis work

1. **Gould** et al. Mean Entropy Predicts Appropriate ICD Therapy Using Cardiac Magnetic Resonance Texture Analysis of Scar Heterogeneity. *European Heart Rhythm Association Conference, Lisbon, Portugal, Poster Presentation; March 2019.*

2. **Gould J** et al. Mean Entropy Predicts Failed Anti-Tachycardia Pacing or Ventricular Fibrillation Using Cardiac MRI Texture Analysis of Scar Heterogeneity. *European Heart Rhythm Association Conference, Lisbon, Portugal, Poster Presentation; March 2019.*

3. **Gould J et al.** Mean entropy predicts ICD therapy using cardiac magnetic resonance texture analysis of scar heterogeneity (YIA Oral Presentation). *Heart Rhythm Congress, Birmingham, UK,* ***Young Investigator Award Runner Up****, Oral Presentation, October 2018.*

4. **Gould J** et al. Dual energy cardiac computed tomography is feasible in guiding optimal left ventricular lead placement in CRT upgrades using coronary venous anatomy, scar and dyssynchrony data. *Heart Rhythm Congress, Birmingham, UK, Poster Presentation, October 2018.*

5. **Gould J** et al. Dual energy cardiac computed tomography to guide optimal left ventricular lead placement in cardiac resynchronisation therapy implantation using coronary venous anatomy, scar and strain. *Heart Rhythm Annual Scientific Sessions Conference, Boston, USA, Poster Presentation, May 2018.*

6. **Gould J** et al. Quantitative assessment of myocardial scar heterogeneity using texture analysis to predict implantable cardioverter defibrillator therapies using cardiac magnetic resonance imaging. *European Heart Rhythm Association Conference, Barcelona, Spain, Oral Abstract Presentation; March 2018.*

7. **Gould J** et al. Dual energy cardiac computed tomography to guide cardiac resynchronisation therapy: a feasibility study using coronary venous anatomy, scar and strain to guide optimal left ventricular lead placement. *European Heart Rhythm Association Conference Barcelona, Spain, Poster Presentation; March 2018.*

Other first author publications arising during period of study

1. **Gould J** et al. Prolonged lead dwell time and lead burden predict bailout transfemoral lead extraction. Pacing Clin Electrophysiol 2019; DOI: 10.1111/pace.13791.

2. **Gould J** et al. Predictors of mortality and outcomes in transvenous lead extraction for systemic and local infection cohorts. Pacing Clin Electrophysiol, 2019; 42:73–84.

3. **Gould J** et al. Transvenous lead extraction in patients with cardiac resynchronisation therapy devices is not associated with increased 30-day mortality. EP Eur 2019; 21:928–936.

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